
# Determination of the Optimal Age to Vaccinate against Dengue Using a Tetravalent Dengue Vaccine in Brazil

**Sandra B. Maier**

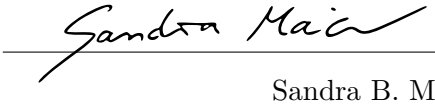
Department of Mathematics and Statistics
University of Strathclyde

A thesis presented in fulfilment of the requirements of the degree of
*Doctor of Philosophy*

September 2019

This thesis is the result of the author's original research. It has been composed by the author and has not been previously submitted for examination which has led to the award of a degree.





Sandra B. Maier
22nd September 2019

# Acknowledgements

First and foremost I would like to thank my supervisor Professor David Greenhalgh for his advice and encouragement during my studies. He has shown me how important honesty and integrity are in research.

I am grateful to my friends from Germany who supported me even from far away and to those friends I met in Scotland. They have made this time unforgettable and their friendship has helped me through the more difficult stages of my PhD.

I would also like to thank my family for believing in me throughout this process and for helping me believe in myself when things were not going as planned. Their support was invaluable.

Finally, I want to thank Juliana who has been there from the beginning. She has endured endless monologues about my work, helped me sift through my ideas and has never lost her patience when I was 'in the zone'. Without her I could not have done this.

# Abstract

Dengue is endemic in most of the subtropics and tropics with half of the world's population at risk of acquiring an infection. For decades only mosquito control could aid with disease prevention. However, in December 2015 the first dengue vaccine, Dengvaxia, became available.

In this thesis a single-serotype transmission model considering the effect of vaccination is derived. Three different assumptions regarding the biting rate are made. Initially, a constant biting rate is assumed to determine the optimal vaccination age for Brazil. For a more accurate description of the dynamics, mosquito biting rate data is used later on to determine an age-dependent rate. Lastly, instead of determining the force of infection from the biting rate, age-dependent serological data is used to estimate both of these functions. The description of the human population dynamics is also improved upon by using a step-death function rather than a constant death rate.

In order to reduce the burden of dengue, the optimal vaccination age is defined to minimise the lifetime expected risk of hospitalisation or lethality. For both risk functions several theories and uncertainties surrounding the disease outcome and the effect of vaccination are studied. The impact of antibody dependent enhancement and permanent cross-immunity on the vaccination age is determined. Additionally, a vaccine-induced increase is incorporated for the risk of hospitalisation. All possible serotype combinations are considered.

The results of this work demonstrate that the optimal vaccination age depends on how the biting rate and force of infection are defined. A variety of different optimal ages for immunisation are found. These vary with the assumptions relating to serotype cross-reactions and depend particularly on whether a vaccine-induced risk is considered. Consequently, a better understanding of the disease and the effect of the vaccine is paramount for finding an accurate optimal age for dengue immunisation.

# Contents

# Published Work

One paper has been published as a result of this work, namely

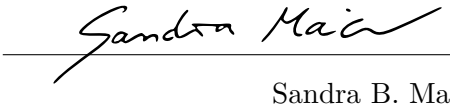
> S. B. Maier, X. Huang, E. Massad, M. Amaku, M. N. Burattini and D. Greenhalgh, Analysis of the optimal vaccination age for dengue in Brazil with a tetravalent dengue vaccine, Mathematical Biosciences 294 (2017) 15–32.

In this article the initial, simplified model with a constant human death rate and a constant biting rate was used to determine the optimal vaccination age for dengue. The underlying model was therefore similar to that which is used in Chapter 4 of this thesis. However, a number of improvements have been made to the work presented in Chapter 4. The discontinuity of the step-wise defined risk functions was eliminated for the purpose of this thesis. The derivation of the basic reproduction number was also revised to include the effect of the extrinsic incubation period. Consequently the effective reproduction numbers derived in the paper and in Chapter 4 of this thesis differ. Due to these differences the optimal vaccination ages are also different.

Additionally, after the publication of the paper it was noted that due to the tetravalence of the vaccine the effects of antibody dependent enhancement and permanent cross-immunity should be considered for any number of co-circulating serotypes. In Chapter 4 more results are therefore presented than in the published paper.

All of these alterations were made before the recommendation regarding the use of Dengvaxia in seronegative recipients were changed so that a vaccine-induced risk was not incorporated.

As the first author of the paper, I have contributed with the development and implementation of the mathematical model, as well as the analysis and interpretation of the results. Additionally, I was responsible for drafting the paper and the incorporation of feedback and comments from the reviewers in the final version.



Sandra B. Maier
22nd September 2019

# List of Abbreviations

| | |
|---|---|
| ADE | antibody dependent enhancement |
| CRS | cross-reaction scenario |
| DDT | dichlorodiphenyltrichloroethane |
| DENv | dengue virus serotype |
| DHF | dengue haemorrhagic fever |
| DSS | dengue shock syndrome |
| PAHO | Pan American Health Organization |
| PCI | permanent cross-immunity |
| SINAN | Brazilian National Notifiable Diseases Information System (Sistema de Informação de Agravos de Notificação) |
| WHO | World Health Organization |

# List of Figures

# List of Tables

Chapter 0

# Outline

An estimated 390 million dengue infections occur globally every year which makes dengue one of the most important vector-borne diseases of our time [165, 166]. While the virus is mostly endemic in tropical and subtropical regions, the changing climate may lead to it spreading to areas that have so far been unaffected. Already over half of the world's population lives at risk of being infected by one of four distinct dengue virus serotypes. Considering the high number of dengue infections and the spread of the virus, the main challenge that we are facing at the moment is the reduction of the burden dengue poses on society. For decades the only means of preventing outbreaks in endemic areas were vector control strategies. However, the first vaccine against dengue, Sanofi Pasteur's Dengvaxia, has been approved recently and is now licensed in several endemic countries. Vaccination could be a great tool in the fight against dengue but for the largest impact it has to be employed in the best possible way.

Brazil is one of the countries that is most affected by the virus and its health care system is under considerable stress each year due to country-wide dengue outbreaks [169]. Control measures aimed at the country's primary dengue vector, the *Aedes aegypti* mosquito, have not led to a relaxation of the situation in recent years. In fact, in the past decade the burden of dengue continuously increased [15]. High hopes are now placed on the new dengue vaccine which has only been licensed in Brazil since December 2015. The aim of this thesis is to determine the ideal vaccination age for dengue in Brazil with this newly-licensed, tetravalent vaccine. However, several uncertainties relating to the serotype interactions as well as the vaccine itself make this a challenging task. With the help of mathematical modelling techniques the optimal age for the use of Dengvaxia in Brazil can be determined. This needs to be done for a multitude of assumptions and scenarios until a clearer understanding of the real dynamics is obtained.

In the first chapter of this thesis background information on the virus as well as on the disease it causes is presented. Some of the key considerations in this chapter are the clinical presentation of dengue and the theories that are being explored as possible explanations for the different disease progressions. Potential prevention strategies and control measures are discussed. The most recent advance in the prevention of dengue is the introduction of the first licensed dengue vaccine, Dengvaxia. An overview of the development of the vaccine and a summary of trial results is therefore given and the current controversy relating to the use in some individuals is reviewed.

The mathematical background is presented in the second chapter and key concepts of epidemiological modelling are explained. Further the challenges associated with the modelling of dengue are discussed and different approaches, which have been used in previously published research, are reviewed.

In the third chapter a modelling framework for the determination of the optimal vaccination age for dengue is presented. A single-serotype transmission model with a general age-dependent human death rate and a general age-dependent mosquito biting rate is introduced. Expressions for the basic reproduction number of the model as well as the force of infection are derived. In order to assess the effect of vaccination the burden of dengue is defined by the lifetime expected risk. This risk is based on the probability of requiring hospital treatment or dying due to dengue. The definition of the lifetime expected risk is further adapted to take account of the possible cross-reactions between antibodies of different serotypes in secondary, tertiary and quaternary infections. Four possible cross-reaction scenarios (CRSs) are defined based on antibody dependent enhancement (ADE) and the possibility of permanent cross-immunity (PCI) after two heterologous infections. Additionally a method allowing for a vaccine-induced risk to be incorporated in the lifetime expected risk is presented.

The general model is simplified in the fourth chapter by assuming constant rates for the death of humans and the rate at which mosquitoes bite humans. A summary of the most important theoretical results under these assumptions is given and serotype-specific effective reproduction numbers are derived from data collected through the Brazilian National Notifiable Diseases Information System (SINAN). Subsequently the optimal vaccination age is determined for the risk of hospitalisation and that of lethality for different assumptions regarding the vaccine efficacy, all CRSs and any number and combination of serotypes. The vaccination age is then limited according to the current licence of Dengvaxia to study the effect of this restriction. The results are discussed and conclusions

regarding their reliability are drawn. In this chapter no vaccine-induced risk is considered since the simulations were carried out before the research community reached a consensus regarding the possibility of such an increased risk.

In the fifth chapter a step-death function for the human population and an age-dependent biting rate derived from mosquito biting data are used. Again important theoretical results are summarised and the effective reproduction numbers are determined for each of the four serotypes. The optimal vaccination ages are computed for the risk of hospitalisation, of hospitalisation with a vaccine-induced risk and for the risk of lethality. Again different underlying assumptions regarding the vaccine, cross-reactions and the endemic area are considered. For each risk function the effect of restricting the vaccination age is examined. The chapter concludes with a discussion of the presented results.

In the sixth chapter a step-death function and an age-dependent mosquito biting rate similar to that in chapter five is considered. However, instead of deriving the mosquito biting rate from biting data and thus the force of infection for a specific vaccination strategy, serological data is used to determine the overall steady-state force of infection of dengue as well as the serotype-specific forces of infection. Subsequently, from the overall force of infection, the age-dependent biting rate is derived. Again the risk of hospitalisation, of hospitalisation with a vaccine-induced risk and of lethality are considered and the optimal vaccination ages minimising these risks are computed for all other underlying assumptions. The vaccination age is then limited according to the licence restrictions as in the previous chapters and the effect of this is discussed. Finally the results are summarised and overall conclusions drawn. The advantage of using serological data as opposed to mosquito biting data is briefly pointed out.

The thesis concludes with an outline of the main results, an analysis of the overall trends for the different assumptions and a discussion of possible further research.

In summary the thesis is therefore structured into seven chapters. The first two chapters provide the reader with the necessary background on dengue and the mathematical techniques that are used throughout the thesis. In the third chapter the modelling framework is introduced in a general manner which is then used to determine the optimal vaccination age in chapters four, five and six for different model assumptions. In the final chapter a summary of the findings is given, overall conclusions are drawn and some possible avenues for future research are discussed.

Chapter 1

# Background on Dengue

## 1.1 Introduction

Dengue is currently considered the most important mosquito-borne disease in the world [165, 166]. One of the reasons for this is that over half of the world's population lives at risk of acquiring an infection with the virus. In fact, more and more previously non-endemic regions are reporting their first outbreaks. The high incidence in endemic regions with a significant proportion of severe cases makes dengue a major public health concern that needs to be addressed. In 2012 the World Health Organization (WHO) devised a global strategy with the aim of significantly decreasing the disease incidence and thus the burden on affected health care systems by 2020 [166]. This global strategy highlights the need for more research and a better understanding of the disease and reiterates the requirement of effective surveillance, prevention and control methods.

In this chapter the current knowledge about the virus and the disease will be summarised. In particular the prevalence of dengue, its clinical features, the lack of specific antiviral agents and possible treatments are discussed. However, it will also be highlighted which aspects of the disease are not yet fully understood and require further research. Of particular interest in this regard are the theories regarding cross-reactions between antibodies of the different serotypes and serotype-specific T-cells. In addition, current and potential prevention and control methods are reviewed. Many advances in the prevention and control of dengue have been made lately and will be pointed out with an emphasis on the recently licensed dengue vaccine Dengvaxia. However, the vaccine has some shortcomings with regard to its use in dengue naive recipients which have been discovered soon after its licensing. The controversy resulting from these findings and their consequences will also be reviewed in this chapter.

## 1.2 Dengue Fever

Dengue is considered a neglected tropical disease. It causes a significant burden on health care systems around the world and more work is necessary to close the current research gaps [81]. In this section an introduction to the dengue virus and dengue fever will be given. To begin with a general overview of the virus and its history is presented. Subsequently the spread and prevalence of dengue is discussed. Additionally, clinical features and treatment methods are assessed. Infection severity varies significantly across reported cases, therefore a classification of the different disease outcomes is presented and the possible reasons for the differences in symptoms and disease progression are discussed.

### 1.2.1 Overview

Dengue is classified as a *Flavivirus* which is a genus of the family *Flaviviridae* and comprises over 75 viruses amongst which are common pathogens such as the yellow fever virus (which is the prototype of the genus), the West Nile virus and the zika virus. Like many *Flaviviruses* dengue is a mosquito-transmitted disease, i.e. blood-feeding, female mosquitoes function as the vector for the virus between hosts. However, the dengue virus stands out amongst other viruses of this genus due to the existence of several genetically and antigenically related but distinct pathogenic serotypes [58, 80, 152]. The different serotypes are believed to have developed from a common ancestor roughly 1,000 to 1,500 years ago [80, 152, 172].

This ancestor and the evolving serotypes were initially maintained in a sylvatic transmission cycle, i.e. with certain arboreal *Aedes* species as vectors and non-human primates as hosts [31, 35, 58, 80, 152, 154]. Today sylvatic dengue cycles persist in Southeast Asia and Western Africa, thus dengue is believed to have originated in one of these regions [80, 152]. The transition from the sylvatic to the human transmission cycles of each of the four dengue serotypes occurred independently and was most likely due to an arboreal vector species feeding on humans in rural areas. Subsequently the virus spread to urban areas where the *Aedes aegypti* and *Aedes albopictus* mosquitoes are its primary vectors and humans serve as hosts [35, 154]. The establishment of a permanent and distinct mosquito-human-mosquito cycle has been determined to only have occurred between 125 and 320 years ago once the urban population was large enough to facilitate it [152, 157, 172]. However, the first description of an infection resembling dengue was recorded in a Chinese encyclopaedia which may date back to the Chin Dynasty (A.D. 265–420). According to Nobuchi [112], as referenced by Gubler [58],

the Chinese referred to the disease as water poison and believed it to be somehow connected to flying insects. This record would roughly coincide with the estimated time of serotype divergence from the common ancestor [80, 152, 172] and could have been caused by a sporadic transmission to humans from arboreal mosquitoes even before a sustained human transmission cycle existed. The first report of an outbreak that actually detailed all symptoms of dengue is thought to be an account by Benjamin Rush [128] of an epidemic of bilious remitting fever or break-bone fever as most of his patients called the disease. It occurred in Philadelphia in 1780, i.e. at a time when a sustained human transmission cycle was potentially well-established.

Following this first account of a dengue epidemic, a number of outbreaks were reported during the 19th century throughout subtropical and tropical regions, e.g. in the Caribbean, India, the United States and Brazil [27, 71, 142]. These are likely to have been caused by the spread in the human cycle through the transmission by *Aedes aegypti* and *Aedes albopictus* mosquitoes. However, these epidemics are attributed to the dengue virus solely based on the description of symptoms that the affected individuals experienced. Considering that the symptoms of a dengue infection can be very similar to those of other febrile illnesses, especially in the early stages of disease progression, it remains unclear whether dengue was indeed responsible for all of them.

The technical advances of the 20th century made it possible to unambiguously identify dengue infections through the isolation of the virus. According to Buchillet [27] the Japanese researchers Kimura and Hotta [89] were the first to isolate the virus from blood samples taken during the epidemic in Nagasaki in 1943. Shortly afterwards, researchers of the United States military also managed to recover the dengue virus during outbreaks in Hawaii and New Guinea [131]. Between 1943 and 1960 four genetically and antigenically related but distinct serotypes were isolated and named dengue virus serotypes 1 to 4 (DENv1–4) respectively [58, 76, 89, 130, 131]. Each of the serotypes can be further subdivided into several distinct genotypes [18, 35]. Chen and Vasilakis [35] reviewed phylogenetic data of a large number of dengue strains and thus identified a total of 20 genotypes (DENv1: 5 genotypes, DENv2: 6 genotypes, DENv3: 5 genotypes, DENv4: 4 genotypes) which are often associated with a specific geographical region.

Recently evidence of a fifth serotype has been discovered which is so far not believed to be a human pathogen [108, 113]. This serotype is often disregarded because it is maintained solely in its sylvatic cycle [31]. It will therefore also be omitted in this thesis since only the human transmission cycle will be modelled.

In 1954, following the successful isolation of the dengue virus, a more severe form of dengue fever was observed in the Philippines; it became known as dengue haemorrhagic fever (DHF) [76]. While this is often cited as the first occurrence of severe dengue (e.g. [58], [55]), Halstead [71] points out that several cases associated with the acute symptoms of DHF and dengue shock syndrome (DSS) had already been recorded at the turn of the previous century. However, after the Second World War an immense increase in dengue incidence and a rise in DHF cases were reported throughout the tropics and subtropics with the virus spreading to previously non-endemic regions [58, 71, 142]. This rapid expansion was likely facilitated by factors such as the population growth in affected areas and an increased urbanisation with little or no preparation of water and sewage systems [58]. Nowadays the fast modes of travel, large numbers of tourists in endemic regions and changing climate are significant risk factors for the virus spreading even further. Indeed, every year dengue infections are recorded in travellers returning from dengue affected countries [162, 165] and more recently even autochthonous infections have been observed in generally non-endemic regions where suitable vectors are present [125, 140, 141, 149]. It is therefore not surprising that dengue is in fact considered a global public health concern that needs to be addressed urgently.

### 1.2.2 Spread and Burden of Dengue

According to recent estimates almost 400 million dengue infections occur annually in dengue endemic areas [22]. In fact, in the past years dengue infections have been recorded in all of the six WHO regions (African region, region of the Americas, South-East Asia region, European region, Eastern Mediterranean region, Western Pacific region) [167]. However, some regions are much more affected than others.

#### African Region

There is no systematic dengue surveillance system in place in countries of the African region and the disease is not officially reported to the WHO resulting in poor surveillance data [165, 166]. This is compounded by several other factors, such as a lack of awareness about dengue and laboratory diagnosis being rare due to a lack of resources [8, 166]. Dengue is also often misdiagnosed as malaria since the symptoms are similar and malaria is highly endemic in the region [8, 148]. Additionally it has been stipulated that the low number of reported dengue

cases may be due to a genetically caused resistance in indigenous Africans [71, 159], i.e. infected individuals show milder symptoms and cases are therefore not reported. Consequently data is insufficient and not accurate enough to draw reliable conclusions about the spread and incidence of dengue. However, recently some research has been carried out to estimate the burden of dengue in Africa from the available case reports by using mathematical modelling methods.

In 2011 Amarasinghe et al. [8] reviewed published literature and databases to estimate the spread of dengue in Africa from case reports. They found that dengue outbreaks have been reported in the majority of the 47 countries in the region. In some countries dengue has only been recorded in travellers. However, they determined that the primary vector, the *Aedes aegypti* is common in all countries which indicates the potential for dengue to become or already be endemic in the entire African region.

Bhatt et al. [22] used a statistical model to determine the risk of dengue around the world. Interestingly, their findings show that the burden of dengue in Africa is comparable to that in the Americas with roughly 16 million infections annually. This contradicts the previous assumption that Asia and the Americas are much more affected than Africa [22, 63, 71]. Messina et al. [105] further evaluated the spread of the four dengue serotypes and found that many countries in Africa have so far reported infections with three serotypes. However, they query whether all of the serotypes are transmitted in a stable human cycle or whether some are only occurrences of infections from the sylvatic cycle.

More research into the spread and burden of dengue in Africa is currently underway [94] and will likely yield a better understanding of the epidemic situation in the region. However, considering the recent findings and the general global situation it is likely that dengue will have a significant effect on the health care systems in Africa in the near future if it does not already [83].

### Region of the Americas

The region of the Americas is one of the regions most affected by dengue in the world [167]. In fact, dengue has been endemic in the region for centuries [40, 142]. Suspected outbreaks occurred as early as 1635 in Martinique and Guadeloupe [142] but due to similarities of symptoms with other febrile illnesses it is unclear whether dengue was indeed the sole cause of these epidemics. The first description of an epidemic detailing all of the symptoms of the disease was recorded in 1780 in Philadelphia [128]. Throughout the 19th century and the first half of the 20th century occasional outbreaks occurred in many parts of the

region, particularly in port cities [40, 142]. It is believed that many of these outbreaks are connected to commercial activities and the importation and spread of the virus and its primary vectors. Dick et al. [40] classified this period from 1600 to 1947 as the period of introduction to the Americas.

Following the proof of the theory that yellow fever is transmitted by the *Aedes aegypti* mosquito by Reed et al. [123] in 1900 eradication efforts were initiated in a number of countries affected by yellow fever (and dengue), e.g. Cuba, Brazil and Colombia [40]. The success of these national eradication programmes and the introduction of the insecticide dichlorodiphenyltrichloroethane, commonly referred to as DDT, led to a continental plan for the eradication of the *Aedes aegypti* which was approved by the Pan American Health Organization (PAHO) in 1947 [42]. In many parts of the Americas this campaign was highly successful, leading to over 18 countries being declared free of the mosquito by 1962 and only a single dengue serotype (DENv2) remaining endemic in the region [40, 57]. Brazil was one of the countries which successfully implemented the plan and eradicated the mosquito in 1955 and after a period of reinfestation again in 1973 [24]. However, in a number of countries such as Venezuela, parts of Colombia and Cuba control measures were less stringently implemented and eradication was not achieved. The persistence of the mosquito and the virus in these regions combined with the gradual decrease in perceived risk in countries that were declared free of the vector led to a resurgence of the vector in most of the Americas in the 1970s and 1980s [40, 57]. The reintroduction of serotypes DENv1, DENv3, and DENv4 to the Americas in the late 20th century resulted in an increasing number of severe cases in the past two decades [40].

Not all countries in the Americas bear a significant burden due to dengue. Case reports from the United States and Canada are rare and usually arise from travellers returning from endemic regions [165]. On the other hand, Latin American health care systems are under a particularly high stress from repeated epidemics. Brazil alone reported roughly 7% of apparent dengue cases in 2010 [22]. Since the reintroduction of DENv4 in 2010 all four dengue serotypes circulate in most of Brazil [105, 134]. Despite repeated efforts by the PAHO to implement vector control strategies and systematic surveillance systems in many countries of the Americas, the region remains one of the most affected by the virus. Large parts of the American region are hyperendemic and are experiencing more frequent and more severe dengue epidemics and thus a higher economic burden [15, 40].

### Eastern Mediterranean Region

Dengue was historically epidemic in many countries of the Eastern Mediterranean region [122]. However, with the introduction of DDT, the population size of the *Aedes aegypti* mosquito dwindled and consequently there were fewer occurrences of dengue fever. In fact, the region was assumed non-endemic for almost half a century until 1985, when an outbreak in Somalia was recorded [122]. Following this re-emergence a number of sporadic outbreaks have been recorded throughout the region [1, 9, 122]. This increase in outbreaks is most likely due to several factors, including the decreased use of DDT, the rapid urbanization with insufficient planning of water and sewage systems in the area, the large number of migrants and tourists, and insufficient vector control measures [9, 122].

The Eastern Mediterranean region is therefore affected by dengue albeit not as much as other regions. In fact, even within the Eastern Mediterranean region there are significant differences in the spread and burden of dengue [166]. Some countries so far appear to be unaffected. However, it is possible that poor surveillance systems in these countries are unable to detect sporadic cases of imported dengue as can be observed in other areas. Particularly countries along the Red Sea and Arabian Sea are affected by the virus and some of them are experiencing dengue as a significant public health problem. The WHO has therefore determined four groups of countries with a similar spread of the disease (Groups A–D, from most affected to unaffected). Between 2008 and 2010 only 1% of all global dengue cases were reported in the Eastern Mediterranean region [22]. However, one reason for a higher number of reported cases in other regions may be better surveillance systems and while the region is not as significantly affected as others it is important to keep in mind that outbreaks in the region are becoming more frequent and devastating.

### European Region

In Europe dengue was non-endemic for most of the $20^{\text{th}}$ century with the last major epidemic having occurred in Greece in 1927 and 1928 [140, 165]. However, dengue is and has been the second most common cause of febrile illnesses in travellers returning from tropical and subtropical countries after malaria [160]. In fact, this importation of dengue cases has now led to a resurgence of the virus in the region. The first autochthonous infections have been reported in the past years in Croatia and France and a large outbreak was recorded in Madeira in 2012 and 2013 [125, 140, 141, 149].

Mathematical modelling studies have shown that the overall risk of dengue

epidemics in mainland Europe is small even though autochthonous infections sporadically occur [95, 100]. However, the changing climate and reintroduction of competent vectors such as the *Aedes albopictus* mosquito give an indication for the risk dengue poses to European countries [125, 140, 160]. The risk is most significant in the Mediterranean area where the higher annual temperatures create a suitable environment for mosquitoes.

Considering the recent re-emergence of the dengue virus it is crucial that the situation is closely monitored, particularly in areas with a higher risk. With only 3,000 reported cases from 2010 to 2013 Europe, nonetheless, remains the region least affected by the dengue virus [160].

### South-East Asia Region

The climatic conditions in South-East Asia are very favourable for the *Aedes aegypti* mosquito due to high temperatures and a heavy rainfall throughout the year in most parts of the region. It is therefore widely distributed and responsible for the disease being highly endemic in South-East Asia [22, 23].

Dengue emerged as a public health problem in South-East Asia shortly after the Second World War [59, 116]. The movement of soldiers during the war facilitated the spread of the *Aedes aegypti* mosquito and the introduction of other virus serotypes to new areas [59, 116]. The resulting hyperendemicity (coexistence of several serotypes) was responsible for the first occurrences of DHF in South-East Asia [59]. A rapid population growth and unplanned urbanisation in the following years aggravated this by creating a highly suitable environment for DHF epidemics due to the high vector density in urban areas with several co-circulating serotypes [59, 116]. 30 years after the war DHF was already a leading cause for hospitalisations and deaths among children in the region [59].

South-East Asia is still disproportionally affected by symptomatic dengue infections and DHF [22, 71, 165] with an estimated 70%-75% of all apparent dengue infections occurring in Asia [22, 165]. The regions of South-East Asia and the Western Pacific are therefore most affected by dengue and bear a huge economic burden [158]. With the frequency and magnitude of dengue epidemics increasing further [143] effective prevention and control strategies are urgently needed.

### Western Pacific Region

14% of all dengue infections that occurred around the world between 2008 and 2010 were reported in the Western Pacific region [22]. The regions is, in fact,

considered to be an epicentre of the disease [106, 167]. Dengue fever and its more severe forms (DHF and DSS) therefore present a significant burden on the health care systems of the affected countries. Most infections are recorded in Cambodia, Malaysia, the Philippines and Vietnam. Roughly 90% of the dengue cases of the region are being reported in these countries [34].

The size and frequency of outbreaks throughout the region has been on the rise ever since it dropped in 1999 and 2000 [16]. This decrease in cases was recorded after a very large outbreak in 1998 and was therefore likely due to a large proportion of the population having been infected during this outbreak. All four dengue serotypes have been reported in the region, with DENv1, DENv2, and DENv3 being more predominant than DENv4 [16, 105].

In light of the increasing number of dengue cases in general and severe dengue cases specifically the WHO devised a strategic plan to reverse the trend of dengue and thus reduce the burden on the health care systems from 2008 to 2015 [168]. Nonetheless, dengue remains a public health problem throughout the Western Pacific region.

**Summary**

Dengue is endemic in five out of the six WHO regions and a threat to the only non-endemic region, Europe, with an increasing number of infections recorded in travellers and the invasion of suitable vector species. Subtropical and tropical regions are particularly affected by the disease with countries in South-East Asia, the Western Pacific and South America experiencing the highest number of reported cases [22, 105, 165]. The true incidence and burden, however, remains unknown. This is true for all endemic areas but most notably so for the African region where there is no surveillance system in place and febrile illnesses are often assumed to be caused by malaria without any laboratory diagnostic. Even in countries where dengue is systematically reported under-reporting and misdiagnosis result in inaccurate data and make the estimation of the true incidence difficult. A coherent comparison between the different regions or even countries within one region is further complicated by the different criteria used for the surveillance of dengue.

According to Bhatt et al. [22] the actual annual number of dengue infections around the world far exceeds that reported to the WHO independent of the region. Messina et al. [105], who evaluated the spread of all four dengue serotypes in the past seven decades, found that Asia and South America bear a high burden of dengue. This is due to the hyperendemicity of the virus in these regions with up to

four coexisting serotypes. However, it cannot be disregarded that the established surveillance systems in these regions may simply be more efficient than those in, for example, the African region. While few cases are reported from Africa it has been estimated that the actual burden may be similar to that recorded in the Americas [22]. The lack of resources for expensive laboratory tests are likely the main reason for little evidence of dengue hyperendemicity in the countries of this region even within the last decade [105].

With the significant spread of dengue, the threat to countries where the virus is so far non-endemic and the high economic burden on affected health care systems it is clear why dengue is considered a global public health concern even without consistent incidence data.

### 1.2.3 Clinical Features and Treatment

Almost 400 million dengue infections occur globally every year. However, most of these infections (roughly 75%) are asymptomatic and go unnoticed [22, 165]. The symptoms and outcome of the remaining 100 million apparent infections vary significantly [165]. Dengue infections are therefore classified based on severity.

Historically it was distinguished between dengue fever syndrome and DHF which could result in DSS [164]. However, since 2009 the practice is to differentiate between dengue fever without warning signs, dengue fever with warning signs and severe dengue [165]. Typical symptoms of a dengue infection include amongst others a sudden onset of fever, aching of the body, headaches, rashes and nausea. These symptoms last between two and seven days and once the fever decreases most patients will recover. However, some patients deteriorate once the fever subsides and enter a critical phase [64, 165]. In this phase patients can, for example, suffer from abdominal pain and tenderness, vomiting, liver enlargement and mucosal bleeding. Patients with these symptoms are considered to experience dengue fever with warning signs. While most of them recover with adequate medical intervention, some cases deteriorate further to severe dengue, i.e. infections with severe plasma leakage with shock, severe bleeding and severe organ impairment.

The reclassification of dengue infections was introduced to assist medical professionals in the triage and treatment of patients with dengue fever [64]. In particular the differentiation between dengue with and without warning signs is supposed to help doctors identify those individuals most in need of close observation. This reclassification seems to be helpful, particularly with respect to identifying patients who can be treated on an outpatient basis [110, 151]. How-

ever, the new system relies more heavily on subjective judgement of the health care professionals, takes the focus of plasma leakage as a sign for severe disease and may lead to a higher economic burden in some countries [147]. Additionally it has been stipulated that the previous classification of dengue infections into dengue fever and DHF may be more practical in epidemiological studies [110].

While the classification of dengue fever has changed, treatment has largely remained the same [164, 165]. In fact, a prompt and adequate treatment can reduce the case fatality rate from over 20% to less than 1% even though no dengue specific therapy exists [58, 165, 167]. In the absence of specific dengue treatments the focus lies on supportive care and management of symptoms, particularly through rehydration.

According to the WHO [164, 165] the main intervention consists of fluid replacement to compensate for the dehydration caused by fever and vomiting. In particular oral fluid intake in the form of fruit juices and fluids containing electrolytes and sugar is encouraged and the patient is closely monitored. However, if this is insufficient an intravenous fluid therapy is administered. The fever and accompanying pain is alleviated with paracetamol. For patients with severe dengue an even closer observation is required and treatment consists of intravenous fluid resuscitation and, if severe bleeding occurs, blood transfusions. The fluid replacement interventions typically lead to a quick recovery of the patient. However, one possible complication of this treatment is a fluid overload which can cause respiratory distress and failure and requires oxygen therapy. Additionally a patient might require treatment of further symptoms of severe dengue, e.g. renal replacement therapy in the case of renal failure.

### 1.2.4 Cross-Reaction Theories

There is a wide variety of disease severity in dengue infections as could be seen in the previous subsection. The reasons for these differences in disease outcome are so far not fully understood. However, they have been theorised to be due to a multitude of interconnected factors associated with the infected individual, the epidemiological situation and the virus itself [65, 72].

Some individual risk factors include the gender of the infected individual, underlying health issues, the age at infection and even the ethnic background. It seems to be the case that males are more prone to DHF than females [146, 155] and that chronic diseases such as diabetes increase the risk of developing severe dengue [52]. However, the effect of age cannot be determined quite as clearly

and seems to depend on the infection history as well [45, 70, 146, 155]. Certain ethnic groups are believed to be less susceptible to severe infections than others [71, 144, 159]. The virus itself is also believed to influence the risk of severe outbreaks with certain serotypes being more prone to lead to serious symptoms such as significant bleeding, haemorrhage and shock [91].

The most important risk factor, however, seems to be the infection history. An increase in DHF/DSS cases around the world has been observed particularly during the second half of the 20th century when fast modes of travel and urbanisation led to the development of hyperendemic regions. The emergence of these severe forms of dengue has therefore been linked to hyperendemicity [58]. However, exactly why the coexistence of several serotypes seems to be responsible for more severe disease outcomes remains to be demonstrated conclusively. There are a number of theories regarding the cross-reactions between antibodies and the different virus serotypes. These theories are namely the lifelong type-specific immunity after infection with any dengue serotype, a short term cross-immunity after an infection, ADE once cross-protecting antibodies decline and PCI after two heterologous infections.

It is generally accepted that an infection with any one of the four dengue virus serotypes confers lifelong immunity to that serotype and cross-protection from infection with heterologous serotypes for a short period [64, 68]. However, the duration of this cross-protection is not known and may indeed vary on an individual basis. Sabin [130] carried out experiments in the 1940s during which he infected and re-infected a group of volunteers with the same or different dengue virus serotypes. He found that cross-protection prevented a re-infection for up to two months and resulted in a milder disease outcome for up to nine months. However, since this study other researchers have found estimates for the period of cross-protection by evaluating outbreak data and case report data using mathematical models. Their estimates range from as little as one week to three years [10, 111, 124]. The discrepancies in these estimates may be due to individual differences, differences in infecting serotypes or the size and accuracy of the data that were used. Sabin's [130] findings strongly indicate a waning effect of cross-protection. Once neutralizing, cross-reactive antibodies decline the individual is therefore fully susceptible to infection with the remaining dengue serotypes.

In fact, 90–95% of all severe dengue infections are attributed to secondary infections and the remaining cases of DHF/DSS are associated with infections in infants that have low levels of maternal antibodies [69, 84, 93]. This observation has been explained by ADE. It is believed that antibodies which developed during

a primary infection or are passed on to the infant from the mother prior to birth are cross-reactive but non-neutralising once the concentration declines. When a heterologous serotype causes an infection the antibodies bind onto the virus without neutralising it and thus facilitate the entry of the active virus into the target cells [84, 87]. Consequently individuals with a secondary infection experience a higher virulence and are more prone to severe symptoms. This theory of ADE has been proposed decades ago [67]. However, until Katzelnick et al. [87] showed the phenomenon in humans in 2017 only in vitro experiments and animal models have supported the theory.

Antibodies from a primary infection cause more severe outcomes in secondary infections. In contrast there is little evidence of enhancement in third and fourth infections. In fact, it is even suspected that the disease is less severe in third and fourth infections. This is based on a small proportion of hospitalisation being due to post-secondary infections [54] and a reduced risk of symptomatic disease after two heterologous infections [72, 115]. It has therefore been theorised that the exposure to two of the four viruses results in a PCI which prevents severe dengue in post-secondary infections [10]. However, it is unclear whether individuals who have experienced two prior infections are completely immune from infection or whether infections are simply asymptomatic or very mild. Wikramaratna et al. [161] used a mathematical model to evaluate this theory and found that asymptomatic infections which contribute to the spread of the disease are more realistic.

In addition to the number of previous infections the risk of severe dengue has also been found to be determined by the exact sequence of serotypes [54] and the time between the first and second infection [10]. Independent of the number of prior infections, serotypes and genotypes with a higher virulence lead to more severe cases, e.g. DENv2 seems to be more virulent than DENv4 while the American DENv2 strain is less virulent than the Asian strain [53].

The antibody cross-reactions not only influence the risk of severe disease in an infected individual. After a large outbreak with one serotype a period of cross-protection leads to less infections overall and the subsequent epidemic is caused by a different serotype once the cross-protection wanes [124]. The next outbreak is unlikely to be due to the same serotype since an infection confers permanent, type-specific immunity and after a large outbreak a significant proportion of the population can be expected to have been infected. Short-term cross-protection, ADE and PCI are therefore also at least partially responsible for multi-annual cycles that can be observed in all hyperendemic regions [165]. In addition ADE

represents a big challenge for the development of vaccines that can effectively prevent outbreaks as will be seen in the following sections.

## 1.3 Prevention and Control

In 2012 the WHO [166] published a global strategy for the prevention and control of dengue. The main goal of this strategy is the reduction of the dengue disease burden by 2020. Specifically the morbidity and mortality of dengue shall be significantly decreased compared to 2010. This goal cannot be reached solely through adequate treatment once an infection is diagnosed so that preventing infections from occurring in the first place will be crucial. Together with the WHO guidelines for the prevention and control of dengue [165] the global strategy outlines all currently available control and prevention measures and the potential of methods which are still being explored.

### 1.3.1 Mosquito Control

Historically the only way of preventing outbreaks and the spread of the dengue virus to new regions was vector control. Its great potential has been shown by the implementation of an *Aedes aegypti* eradication plan in the 1950s and 1960s in large parts of the Americas. Despite the eventual abandonment of the plan vector control strategies remain the most important tool for the prevention of dengue and many other mosquito-borne diseases.

Most mosquito control strategies can be categorised into environmental (physical), chemical and biological approaches [165]. Their general purpose is to prevent the transmission of the virus which can be achieved either by avoiding contact between mosquitoes and humans or by decimating the mosquito population. The WHO [165] recommends an integrated vector management approach combining environmental, chemical and biological methods. Such an approach ensures a cost-effective employment of resources and the sustainability of implemented vector control measures.

#### Environmental Control

Environmental control is probably the most elementary approach of preventing disease transmission by mosquitoes. Long-established and commonly used methods that reduce the number of vector-host contacts rely on the change of human behaviour and alterations to habitations [163, 165]. Individuals can, for

example, avoid mosquito bites by wearing light-coloured, long-sleeved clothing, by using mosquito nets when sleeping and by staying indoors during the hours of high mosquito activity. The risk of being bitten can further be reduced through the installation of screens on all windows and doors.

The mosquito population can be targeted through long-lasting modification and manipulation of its habitats, particularly its larval breeding sites [163, 165]. The size of the population can effectively be reduced by hindering mosquitoes from accessing adequate habitats. One way of achieving this is the mosquito-proofing of water tanks and cisterns. The installation of a reliable water infrastructure, however, is preferable since it can make the use of cisterns obsolete. Independent of the mode of water supply it is important to regularly empty, clean or remove other water containers such as plant pots, drinking bowls for animals and any discarded objects which may function as a breeding site. Old tyres are a prime example for such objects in urban settings. In general an improvement of waste disposal practices helps with the reduction of larval breeding sites.

### Chemical Control

The transmission of dengue can also be controlled by chemicals such as insecticides and chemical repellents [39]. There are two categories of insecticides which target the mosquito at different developmental stages [165].

Larvicides are used to interrupt the growth cycle or kill mosquito larvae before they can reach the adult stage. They are commonly applied to larval habitats such as water tanks and also affect adult mosquitoes that come into contact with them. A number of chemicals exist that can be used for mosquito control, even for drinking water as long as the dosage does not exceed a critical value. The majority of larvicides, however, can only be applied to non-potable water. Due to the toxicity of all larvicides they should only be used sparingly and when environmental methods are not sufficient for an effective vector control [165].

Adulticides, on the other hand, are chemicals used to kill fully developed mosquitoes. The spraying of surfaces in and around houses with insecticides that have a long-lasting effect is known as residual treatment. In contrast the dispersion of an insecticide into the air in the form of fog is referred to as space spraying. During large outbreaks this method is particularly useful due to its immediate effect and the possibility of rapidly covering large areas if aerial spraying is carried out.

While insecticides are a powerful tool for the control of mosquito populations they do have some flaws. All insecticides are toxic and should therefore be used sparingly and under consideration of the damage they might cause to other species

and the environment [14, 165]. Additionally there is a possibility of mosquitoes developing a resistance to the chemicals. This has indeed already been observed for a number of insecticides such as DDT which is no longer as effective in reducing the number of mosquitoes as it once was.

### Biological Control

The focus of control methods is gradually shifting from chemical to biological control measures. This shift is due to the development of insecticide resistance in *Aedes aegypti* mosquitoes and an increased awareness of environmental issues [20].

Classical biological approaches for the control of mosquito populations revolve around the introduction and maintenance of predatory species to larval habitats [20, 165]. Such predators are, for example, certain species of small fish and copepods which feed on the larvae of mosquitoes. Extracts from plants are another capable and ecologically friendly means of reducing the mosquito population size when used as insecticides and can also be used for the prevention of vector-host contacts in mosquito repellents. Interestingly even other pathogens can be used to control and prevent dengue infections [14, 20]. Some types of fungi, for example, can act as insecticides for which resistance will take much longer to develop than for classical chemical pesticides.

The most researched pathogen that shows a large potential for the control of dengue outbreaks is a genus of bacteria called *Wolbachia*. In fact, different *Wolbachia* strains offer a variety of control mechanisms due to their distinct effects on the infected mosquito populations [14, 20, 171]. Many strains result in infected mosquitoes having a reduced fitness either due to a shortened life-span or due to a decrease in reproductive rate. In either case the result is a reduced population size. Other species do not necessarily influence the mosquito's fitness but instead affect its ability to transmit dengue. Dependent on the strain the inhibition of virus transmission can be almost complete. However, the potential risks and benefits of a widespread *Wolbachia* introduction are not yet fully explored [20].

Another method of biological control that is being explored is the sterile insect method, i.e. the release of a large quantity of sterile males into wild populations. There are a variety of approaches for the sterilisation of mosquitoes such as chemical agents and radiation. Genetic engineering can also be used to insert a lethal gene into the mosquito population that can be repressed in the carrier but will lead to inviable offspring in the wild.

Many of the biological control measures have the advantage of being less prone

to induce a resistance in mosquitoes. An additional advantage is the possibility of specifically targeting certain mosquito species. This is the case particularly with the newer methods using genetically modified or sterilised males. However, even with these promising biological methods the focus should remain on a sustainable integrated vector management.

### 1.3.2 Vaccination

The most powerful tool in the prevention and control of infectious diseases is widely considered to be vaccination [117]. Its biggest success story is undoubtedly the complete eradication of smallpox on a global scale in 1977 [126]. This eradication was achieved due to an effect known as *herd immunity*, i.e. even individuals who have not received the vaccination are protected due to the interruption of the transmission in vaccinated individuals [13]. In the absence of a non-human reservoir *herd immunity* eventually results in complete eradication. So far smallpox remains the only disease for which this has been achieved but significant advances have been made in the control of many other diseases. The number of polio, measles and rubella cases, for example, could be decreased immensely through the use of vaccines. In general vaccination has contributed to a decline in infant and childhood mortality and reduced the economic burden infectious diseases have on our society [13].

Naturally for a disease like dengue, which affects millions of people annually, the possibility of vaccination must be considered. However, the existence of four distinct but closely related serotypes and the limited knowledge regarding their interactions have made the development of such a vaccine challenging [118]. Despite first steps towards a dengue vaccine being taken in 1945 it took scientists decades of research and investments totalling over a billion dollars [61] to develop vaccine candidates ready for large-scale human trials. Only in the last decade have a handful of promising vaccine candidates reached clinical phase three trials. One of these candidates – a tetravalent, live-attenuated, chimeric vaccine which was developed by Sanofi Pasteur – was finally licensed under the name Dengvaxia for the use in endemic countries in December 2015 [61, 118].

A safe and efficacious vaccine is expected to significantly decrease the burden of dengue and may also help limit the spread of the virus. Dengvaxia therefore is a promising control tool for dengue. However, the licensing of the first ever dengue vaccine has not yet resulted in the hoped-for effect. Instead, a controversy has ensued about its safety. The development, trial results and the controversy surrounding Dengvaxia will be discussed in detail in the next section.

## 1.4 Dengvaxia – The First Dengue Vaccine

72 years after the dengue virus was initially isolated the first vaccine against the disease finally became available in 2015 [13, 61]. However, it took over 20 years of research, huge financial investments and a number of clinical trials before this point was reached and Dengvaxia could be marketed. The development process and the results of several clinical trials which eventually led to the licensing of the vaccine will be reviewed in this section. Additionally, the controversy that arose shortly after its introduction will be outlined and its consequences discussed.

### 1.4.1 Development and Licensing

Dengvaxia, like any vaccine, has had to pass through a number of developmental stages before its approval in 2015. Sanofi Pasteur, the manufacturer of the vaccine, started the development of Dengvaxia in 1998 when the possibility of using a yellow fever vaccine strain as a backbone was proposed [60, 61]. Four recombinant dengue strains named CYD1–4 were constructed from wild-type DENv1–4 strains and eventually combined into a tetravalent vaccine which was referred to as CYD-TDV prior to being licensed as Dengvaxia [60]. What followed was a lengthy process of pre-clinical and clinical trials in which the safety and efficacy of the vaccine candidate had to be demonstrated.

Pre-clinical trials were carried out to demonstrate the phenotypic and genotypic stability of the vaccine strains and to asses the vaccine candidate's ability to induce an immune response. Additionally a number of theoretical risks had to be evaluated. In particular the likelihood of vaccine strain transmission by mosquitoes, the reversion to virulence of the yellow fever backbone, the recombination of the vaccine strains with wild-type strains and the possibility of vaccine-induced ADE needed to be determined. During this early developmental stage the vaccine candidate was assessed in vitro on non-human and human cells and in vivo on non-human primates only. A number of non-clinical safety studies were also carried out to determine safety factors such as the toxicity of the vaccine. The results from the pre-clinical phase indicated a satisfactory safety and immunogenicity profile for CYD-TDV and did not show any cause for concern relating to the identified theoretical risks [60, 61]. However, with respect to ADE pre-clinical test did not yield definite results and it was assumed that it would only be possible to identify the risk for recipients due to ADE in later stages [60].

The results from the pre-clinical phase enabled the vaccine candidate to progress to the clinical development. In a first step small cohorts of volunteers in

endemic and non-endemic countries were vaccinated and the immune response and safety evaluated. These clinic phase one trials indicated that recipients developed antibodies to all four dengue serotypes after three doses of the vaccine and that the ideal time between the individual doses was six months. In the clinical phase two and phase three trials which followed larger trial cohorts were therefore vaccinated at 0, 6 and 12 months. The main purpose of the phase two and phase three trials was the assessment of the vaccine efficacy and safety under actual disease conditions [61]. The safety and efficacy that was determined for Dengvaxia as part of these trials will be discussed in more detail in the next section. However, the outcome of the trials was positive and therefore resulted in the approval of the vaccine in December 2015 [136].

Despite the licensing of the vaccine the clinical phase of the development is still ongoing today. In particular the long-term follow-up of trial participants is intended to be continued until up to five years after the last dose was administered and further phase four trials will be carried out [61]. The aim of this continuous evaluation is to determine the long-term efficacy and to detect any adverse events that did not manifest in the trial cohorts but may become apparent once a large number of individuals has been immunised with Dengvaxia.

### 1.4.2 Efficacy and Safety

The efficacy and safety of Dengvaxia was evaluated in a number of studies. However, three clinical trials in particular are of interest as their results were used to determine the efficacy and safety of the vaccine. Those trials are an extended phase two trial with a study cohort of over 3,000 Thai schoolchildren aged between 4 and 11 years (CYD57 trial, extended from CYD23 trial) [66, 129] and two phase three trials with a combined study cohort of over 30,000 children between the ages of 2 and 16 years from five different locations in the Asian-Pacific region (CYD14 trial) [32] and from five Latin American countries (CYD15 trial) [156]. For the CYD14 trial children between the ages of 2 and 16 years were recruited, while for the CYD15 trial only those above the age of 9 years were considered. In each of the trials the cohort was randomly divided into a vaccine group and a control group at a ratio of 2:1 where the assignment was stratified by age. An additional immunogenicity study was carried out for a subgroup of participants. Participants in the vaccine group received three doses of Dengvaxia at an interval of 6 months and active surveillance lasted until month 25 of the trials.

### Efficacy

Hadinegoro et al. [66] evaluated the data that was collected during the CYD14 and CYD15 clinical trials to determine the efficacy of Dengvaxia. They found that the effectiveness of the vaccine against virologically confirmed dengue is dependent on a number of factors, namely the infecting serotype and the serostatus and age of the recipient at baseline. The vaccine was found to be least effective against infections with DENv2 and most effective against DENv4 if all recipients were considered. However, for young recipients it was more effective against infection with DENv3 than with DENv4. Independent of the age of the recipient the vaccine performed better in seropositive than in seronegative individuals. This effect was still influenced by age with a larger difference between younger individuals with or without previous infection than in older individuals. A summary of these results is presented in Table 1.1. The efficacy is shown according to the serotype or the serostatus of the recipient at baseline for individuals of any age and for the two age-groups of 2–8 year-old individuals and 9–16 year-old individuals.

The age and serostatus of the recipient at baseline are correlated with an increase in the number of seropositive individuals at higher ages. This leads to the question whether the higher efficacy in the older age group is indeed caused by the age per se or whether the age is merely a surrogate for serostatus, i.e. the higher efficacy is caused by more individuals of this age-group having experienced a prior infection [61]. Potentially a combination of both the age and the serostatus causes the observed efficacy profile of Dengvaxia. The age of the recipient may, for example, influence the immune response due to the physiological development at younger ages being incomplete [61].

Table 1.1: Vaccine efficacies for Dengvaxia by serotype or serostatus at baseline. Efficacies are shown for all ages pooled and separately for ages below 9 years and 9 years and older as presented by Hadinegoro et al. [66].

| | Pooled | 2 – 8 years | 9 – 16 years |
|---|---|---|---|
| **According to serotype** | | | |
| DENv1 | 54.7% | 46.6% | 58.4% |
| DENv2 | 43.0% | 33.6% | 47.1% |
| DENv3 | 71.6% | 62.1% | 73.6% |
| DENv4 | 76.9% | 51.7% | 83.2% |
| **According to serostatus** | | | |
| Seropositive | 78.2% | 70.1% | 81.9% |
| Seronegative | 38.1% | 14.4% | 52.5% |

### Safety

The safety of the vaccine was determined in the CYD57, CYD14 and CYD15 trials during the active phase, i.e. 25 months after the last dose was administered [32, 129, 156]. Dengvaxia was determined to be safe since in none of the trials an increase in severe adverse events was recorded for participants in the vaccine group compared to those in the placebo group. Additionally the clinical presentation of individuals who became infected with dengue was either found to be similar in the vaccine and control group [129, 156] or indeed milder in vaccine recipients experiencing breakthrough infections [32]. Despite the promising safety profile that was observed in the active phase of these trials the safety analysis was intended to continue for up to 5 years after the last dose was administered.

Hadinegoro et al. [66] carried out an initial evaluation of this extended safety follow-up in 2015 to determine the long-term safety of Dengvaxia. By this time data covering years three and four for CYD57 and year three for CYD14 and CYD15 were available. They found no overall differences of safety between the vaccine and control groups in any of the trials that would indicate a safety concern. Frequency of adverse events and clinical presentations in breakthrough infections were similar for both cohorts. However, when a post-hoc analysis of the two age-groups of participants below or above the age of 9 years was carried out an increased risk of adverse events was observed for younger vaccine recipients compared to the control group of the same age. The results from years three and four of the CYD57 trial indicated that this increase in severe adverse events may only be observed for a short period. However, due to the much higher safety in older recipients approval was eventually sought for the use in individuals above the ages of 9 years only.

The licensing of Dengvaxia was highly impacted by the safety analysis of the vaccine. This was the case despite a relatively limited indication for safety issues. Due to a detailed post-hoc analysis of the vaccine safety in recipients of certain age-groups the licence for Dengvaxia was only sought for children above the age of 9 years. However, despite the post hoc analysis not all factors impacting the safety in specific recipients could be analysed, particularly the effect of serostatus was not easily evaluated. In fact, despite the age-restriction that was the result of the safety analysis concerns were raised by a number of researchers shortly after the licensing of the vaccine and eventually a controversy regarding the use of the vaccine ensued. This controversy and its outcomes will be discussed in detail in the next subsection.

### 1.4.3 Controversy

The licensing of Dengvaxia in December 2015 was a promising step towards reaching the goals the WHO set for the reduction of the global dengue burden. However, first indications for safety concerns relating to the use of Dengvaxia were noticed during the long-term follow-up of the CYD57 phase two trial [66]. During year three of this study an increased number of hospitalisations due to virologically confirmed dengue was reported in younger vaccine recipients compared to the individuals of the same age in the control cohort. Meanwhile, for trial participants above the age of 9 years no safety risk was demonstrated.

Guy and Jackson [62] stipulated that the increased risk in breakthrough infections in younger individuals may have been due to the serostatus rather than the age of the recipient. Younger children are more likely not to have experienced a prior infection at the time of vaccination. They argued that a wild-type dengue infection in seronegative vaccine recipients is similar to a secondary type infection and therefore more severe. While this may only be a temporary effect insufficient data was available at the time to confirm or disprove an overall long-term risk in this age-group. The vaccine was therefore licensed only for the use in individuals above the age of 9 years.

The WHO [132] recommended the use of the newly licensed vaccine in endemic settings with at least 50% of the targeted population being seropositive. A very high endemicity with a seroprevalence of 70% or more in potential recipients was considered to be a good indicator for the use of Dengvaxia. However, they also pointed out that the long-term follow-up of several clinical trials had shown an increased number of hospitalisations and severe dengue cases in vaccinated individuals compared to the control group. Table 1.2 presents the number of hospitalisations and severe dengue cases as reported by the WHO [132] in April 2016.

Table 1.2: Number of hospitalisations and severe dengue cases in the vaccine and control group by age and serostatus at baseline recorded during the long-term follow-up of Dengvaxia trials [132].

| | Pooled | 2 – 8 years | 9 – 16 years |
|---|---|---|---|
| **Control Group** | | | |
| Seropositive | 26/988 | 11/236 | 15/752 |
| Seronegative | 9/377 | 5/173 | 4/204 |
| **Vaccine Group** | | | |
| Seropositive | 16/2,027 | 9/481 | 7/1,546 |
| Seronegative | 24/712 | 17/330 | 7/382 |

An increased risk for adverse events was therefore particularly high in seronegatives below the age of 9 years. Consequently the WHO warned of possible risks associated with the use of Dengvaxia in young children and only recommended its use in individuals above the age of 9 years. They also noted that there is the possibility of seronegative recipients experiencing an increased risk independent of their age and called for further analysis of the long-term safety particularly for seronegative recipients. They did not, however, limit their recommendation to seropositives.

The recommendations of the WHO were quickly criticised by the wider research community (e.g. [6, 38, 74]). Dans et al. [38] questioned the analysis based on the age-groups altogether particularly with respect to the threshold at 9 years and warned of the possible effects of vaccine-induced ADE. Other key questions that were raised were whether the poorer performance of Dengvaxia in younger individuals during the long-term follow-up of the clinical trials was due to the age of the recipient per se or actually caused by their serostatus and whether vaccine-induced ADE was to blame for this risk [4, 75]. By using the age as a surrogate for serostatus the increased risk in older seronegatives was underestimated and the possibility of an increased risk for seronegative recipients of any age was not conclusively refuted. It was therefore argued that the vaccine should not be administered to individuals with an unknown infection history.

Only a small number of trial participants had been tested for antibodies prior to the administration of the vaccine [133]. Under the mounting pressure statistical methods were used to infer the serostatus at baseline of all trial participants to determine the risk seronegative recipients were exposed to due to vaccination [133]. This post-hoc analysis confirmed an increased risk in all negative vaccine recipients [139] and eventually resulted in a revision of the recommendation made by the WHO [133] and a change of the vaccine's label [135]. Despite this Sanofi Pasteur and the WHO still argue that the overall population level benefit in endemic settings with a very high seroprevalence amongst the targeted population (at least 80%) could justify an increased risk in some recipients [133, 135]. Aguiar [2] strongly opposes this view on ethical grounds as no individual should be put at risk by receiving the vaccine. The prevailing opinion is that Dengvaxia should only be administered to seropositive individuals aged 9 years or above after their serostatus was confirmed by a laboratory test. Indeed, this is the current recommendation of the WHO [133].

This controversy is amplified by the fact that two large-scale vaccination campaigns were already under way in the Philippines and in Paraná State in Brazil

by August 2016 [137, 138]. In total well over 1 million children and adults were targeted as part of the two programmes. The national campaign in the Philippines was halted shortly after Sanofi Pasteur confirmed the possibility for an increased risk in some recipients [43]. However, over 800,000 schoolchildren had already received the vaccine by that point and it is assumed that 80,000 of them are now at an increased risk for severe dengue [43]. The public opinion of vaccines against dengue and indeed vaccines in general suffered significantly in the Philippines as a consequence of the hasty implementation of the campaign and its subsequent discontinuation [92]. Policy makers and vaccine manufacturers have a wide-reaching responsibility when it comes to the licensing and distribution of vaccines. In the case of Dengvaxia, despite warning signs, these responsibilities may not have been fully considered. However, other vaccine candidates may benefit from the controversy as it highlighted the need for a better analysis of the serostatus of recipients.

## 1.5 Summary

In this chapter the current knowledge regarding the dengue virus and the disease it causes has been presented.

A general overview of the virus was given and the spread and burden in the different WHO regions was discussed. The symptoms and treatment methods of dengue have also been reviewed. The absence of specific treatment methods was noted. In fact, medical intervention usually consists of fluid replacement to prevent dehydration and management of symptoms. However, a wide range of symptoms can be observed which has led to a number of theories regarding the cross-reactions of different serotypes and antibodies that were developed during a previous infection. Some of these theories are commonly accepted, such as the life-long type-specific immunity following recovery from an infection. However, a possible cross-protection and its consequences are still being discussed. Most notably the phenomenon of ADE has been used to explain the fact that most severe dengue cases are recorded during secondary infections.

It was noted that in order to accomplish a significant reduction in disease burden the prevention and control of dengue is of paramount importance. Mosquito control methods were discussed in detail since historically they were the only tool of controlling disease outbreaks and the spread of the virus to new regions. However, significant advances towards a dengue vaccine have been made in the past 20 years and cumulated in the licensing of the first ever dengue vaccine,

Dengvaxia, in 2015. With promising safety and efficacy results in clinical trials much hope was placed in this vaccine. In fact, it has been shown that the vaccine is capable in aiding with the reduction of the dengue burden. However, safety concerns in some recipients have resulted in a controversy and a careful analysis of long-term data is necessary to determine the potential benefit of the vaccine on an individual and population level.

Of particular importance in this chapter were the cross-reaction theories relating to ADE and PCI which will be reconsidered in Section 3.4 to determine the population level risk of dengue. Additionally the efficacy data and the data relating to the relative risk according to serostatus as presented in Tables 1.1 and 1.2 will be used throughout this thesis for the determination of the optimal vaccination age with Dengvaxia in Brazil. However, the increased risk in seronegatives will not be considered in all simulations since a broad consensus regarding this risk was only reached at the end of 2017. In Chapter 4 only optimal vaccination ages under the assumption of no vaccine-induced ADE will therefore be considered, while in the following chapters the recent developments are included in the assumptions.

Chapter 2

# Mathematical Background

## 2.1 Introduction

Mathematical models are a simplified representation of real world systems and dynamics. They are used to describe and understand complex systems, to predict the impact of changes on their dynamics, and to control or optimize the outcome of a process. Today such models can be found in almost any discipline including mathematical biology and epidemiology where they serve to understand population dynamics and the spread of infectious diseases.

In this chapter the epidemiological modelling approaches that form the basis for the following chapters will be presented. In particular the most important techniques with respect to compartmental models are discussed and explained. The use of the mass action law in epidemiological modelling was the first step towards this type of model and will therefore be of particular interest. It is the foundation for a multitude of Ross-MacDonald type models which describe mosquito-borne infections today. With advances in the modelling techniques also came a number of important concepts such as the basic reproduction number and the force of infection which are paramount to epidemiological modelling. These key concepts are presented as well.

Dengue is a mosquito-transmitted disease and therefore commonly modelled with the help of Ross-MacDonald type models. However, a unique set of challenges is associated with the modelling of this particular disease and uncertainties regarding its dynamics exist. A wide variety of research questions in combination with these uncertainties have led to a range of different models. A discussion of the most common dengue modelling approaches will therefore conclude this chapter.

## 2.2 Epidemiological Modelling

The first use of mathematical models in the understanding of infectious diseases is commonly attributed to Daniel Bernoulli for his work on smallpox mortality in 1766 [21]. He used his model to show that inoculation against smallpox has a positive effect on the life expectancy at birth. In 1911, almost 150 years later, Ross [127] published his work on malaria control which paved the way for modern mathematical epidemiology. The underlying theory for the compartmental model he described in this seminal work is known as the mass action law. Ross's model was built upon by the likes of Kermack and McKendrick [88] and MacDonald [97]. Certain compartmental models describing transmission dynamics of indirectly transmitted diseases are now known as Ross-MacDonald type models due to the impact Ross and MacDonald had on the study of vector-borne diseases.

### 2.2.1 The Law of Mass Action

One of the most important principles in epidemiological modelling is the law of mass action. In a chemical context this law states that the rate at which a reaction between two substances takes place is directly proportional to their concentrations. Ross [127] implicitly applied this theory to epidemiology by assuming that the rate at which susceptibles become infected is proportional to the rate at which they come into contact with the infectious agent.

There are two commonly adopted interpretations of this principle which are referred to as pseudo and true mass action [19, 104]. By denoting the number of susceptible and infected individuals at time $t$ by $S_H(t)$ and $I_H(t)$ and the total number of humans by $N_H(t)$, the number of newly infected individuals per unit of time $\mathrm{d}t$ are given by

$$\beta'_H I_H(t) S_H(t)\,\mathrm{d}t \qquad \text{and} \qquad \beta_H \frac{I_H(t)}{N_H(t)} S_H(t)\,\mathrm{d}t \tag{2.1}$$

respectively for the two interpretations assuming a direct transmission of the disease. $\beta'_H$ and $\beta_H$ are both transmission constants that describe the probability that a contact between a susceptible and an infected individual occurs and that such a contact results in transmission. The probability of transmission during contact is the same in both cases. However, in the case of pseudo mass action the contact rate is assumed to increase as the total population density increases, whereas for true mass action it is assumed that this rate does not dependent on the density of the population. Consequently $\beta'_H$ and $\beta_H$ differ. Based on

the underlying assumption relating to the contact rate it has been suggested that *density-dependent transmission* and *frequency-dependent transmission* more adequately capture the nature of the modelled dynamics than pseudo and true mass action [19].

Many directly transmitted diseases can be modelled with a density-dependent transmission term. However, some directly transmitted infections, particularly sexually transmitted diseases, are more suitably modelled with a frequency-dependent transmission term. Vector-transmitted diseases should also be modelled using a frequency-dependent approach [104]. In particular the rate of contact between susceptible humans and infectious mosquitoes must be independent of the host density to ensure that the transmission depends on the likelihood that a vector has had a prior contact with an infected individual. The contact rate in the mosquito population must depend on the probability of contacting an infected human but not on the mosquito density. Thus the law of mass action, when frequency-dependent transmission is considered, yields the number of newly infected humans and mosquitoes per unit of time $\mathrm{d}t$ as

$$\beta_H \frac{I_M(t)}{N_H(t)} S_H(t)\,\mathrm{d}t \qquad \text{and} \qquad \beta_M \frac{I_H(t)}{N_H(t)} S_M(t)\,\mathrm{d}t \tag{2.2}$$

respectively. Here $N_H(t)$, $S_H(t)$ and $I_H(t)$ denote the number of humans, the number of susceptible humans and the number of infected humans respectively and $S_M(t)$ and $I_M(t)$ similarly denote the number of susceptible mosquitoes and infectious mosquitoes. $\beta_H$ denotes the transmission rate between infectious mosquitoes and susceptible humans and $\beta_M$ that between infected humans and susceptible mosquitoes, both of these are based on constant contact rates.

The use of this theory in epidemiological modelling paved the way to modern mathematical epidemiology. However, it is important to recognise that this principle is based on homogeneous mixing in the studied population [145]. By applying the law of mass action the underlying assumption for the mathematical model is that all susceptible and infected individuals are equally likely to meet (or get in contact with a vector) and that every individual is equally likely to contract or transmit the disease during such an encounter. This is a simplifying assumption and does not necessarily describe every disease or population realistically. Nonetheless, models that are based on the principle of mass action, such as Ross-MacDonald type models, can provide valuable insights into transmission dynamics [17].

### 2.2.2 Ross-MacDonald Type Models

Classical Ross-MacDonald type models describe the transmission of vector-borne diseases through a set of ordinary differential equations. The populations of humans and vectors are divided into several compartments which correspond to different states of infection, such as susceptible, exposed, infected or recovered. For his malaria model Ross [127] proposed susceptible and infected compartments for each of the populations. However, other researchers later extended the number of compartments for both populations. MacDonald [97] was the first to include an exposed or latent state for the mosquito population based on biological observations showing that mosquitoes which are exposed to the malaria parasite only become infectious after a short period of time. Compartments for exposed or latent and recovered humans were also added to some models [98]. The inclusion of further compartments increased the accuracy of the malaria model, but even with Ross's model the basic dynamics could already be captured. For other diseases certain compartments are necessary to adequately describe the dynamics. For a single-serotype dengue model, for example, the lifelong type-specific immunity can only be captured by including a recovered compartment in the human population. Independent of the number of compartments the underlying theories and assumptions are often very similar.

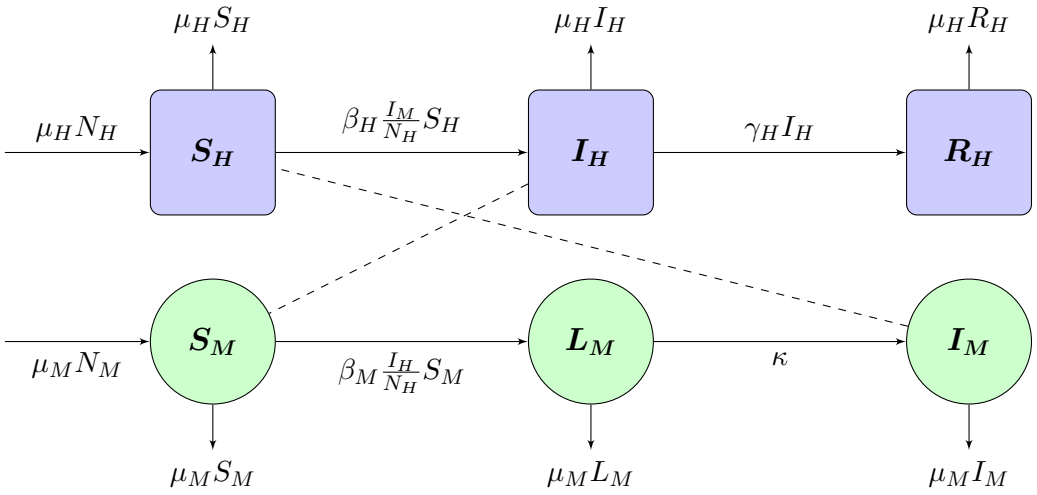



Figure 2.1: Illustration of a Ross-MacDonald type model with compartments for susceptible, infected and recovered humans and susceptible, exposed and infectious mosquitoes.

Consider the Ross-MacDonald type model that is illustrated in Figure 2.1. The human and mosquito populations are each divided into three compartments, namely susceptible, infected and recovered or immune for humans and susceptible, latent and infectious for mosquitoes. The total number of individuals in each species is obtained as the sum of the individuals at all three stages of infection.

First consider the human population. The number of susceptible humans at time $t$, $S_H(t)$, changes as new individuals are born into the compartment, susceptibles become infected or leave the compartment upon their death. The number of infected humans $I_H(t)$ increases due to newly infected individuals recruited from the susceptible compartment but decreases due to recovery from infection and death. The number of recovered humans, $R_H(t)$, consequently increases as infected individuals recover and decreases due to the death of recovered individuals.

$\mu_H$, the rate at which humans die, is constant and equal for all compartments. No additional deaths are assumed to be caused by the disease. Generally Ross-MacDonald type models tend to assume a constant population size. In order to achieve this the birth rate for the human population also needs to be given by $\mu_H$. In the model depicted in Figure 2.1 all newborns are recruited into the susceptible class, i.e. the disease is not transmitted vertically and antibodies are not passed on from the mother to the child.

Susceptibles become infected according to the law of mass action. For vector-transmitted diseases a frequency-dependent transmission is commonly assumed [104], i.e. the number of newly infected individuals per unit of time is given by $\beta_H \frac{I_M(t)}{N_H(t)} S_H(t)\,\mathrm{d}t$ where $\beta_H$ is the per capita rate at which transmission between susceptible humans and infectious mosquitoes occurs. Once infected, individuals are assumed to recover at a constant rate $\gamma_H$. Recovered individuals leave the recovered compartment only when they die so that a disease without waning immunity or the possibility of reinfection is described by the model. The governing equations for the human population shown in Figure 2.1 are therefore given by

$$\begin{aligned}
\frac{\mathrm{d}S_H}{\mathrm{d}t} &= \mu_H N_H(t) - \beta_H \frac{I_M(t)}{N_H(t)} S_H(t) - \mu_H S_H(t), \\
\frac{\mathrm{d}I_H}{\mathrm{d}t} &= \beta_H \frac{I_M(t)}{N_H(t)} S_H(t) - \gamma_H I_H(t) - \mu_H I_H(t), \\
\frac{\mathrm{d}R_H}{\mathrm{d}t} &= \gamma_H I_H(t) - \mu_H R_H(t), \\
N_H(t) &= S_H(t) + I_H(t) + R_H(t).
\end{aligned} \tag{2.3}$$

For the mosquito population the size is also assumed to be constant in time. Vertical transmission is not considered to take place in the model shown in Figure 2.1. Again the disease does not have any impact on the death rate which is given by $\mu_M$ for all compartments. The number of susceptible mosquitoes $S_M(t)$ increases by $\mu_M N_M(t)\,\mathrm{d}t$ mosquitoes in a small time interval of length $\mathrm{d}t$ to ensure a constant population size. The law of mass action is again applied with a frequency-dependent transmission. $\beta_M$ therefore denotes the rate of transmission from infected human to susceptible mosquito. However, mosquitoes do not immediately transmit the virus once they contract it. Instead, once a mosquito has been infected it will only start transmitting the virus after an incubation period $\tau$. Therefore only exposed mosquitoes that survive this latency period become infectious, i.e. the number of newly infectious mosquitoes per unit of time is given by $e^{-\mu_M\tau}\beta_M\frac{I_H(t-\tau)}{N_H(t-\tau)}S_M(t-\tau)\,\mathrm{d}t$. Infectious mosquitoes only leave the compartment once they die. This is attributed to the short life-span of mosquitoes. Hence the mosquito population is mathematically described by

$$\begin{aligned}
\frac{\mathrm{d}S_M}{\mathrm{d}t} &= \mu_M N_M(t) - \beta_M\frac{I_H(t)}{N_H(t)}S_M(t) - \mu_M S_M(t),\\
\frac{\mathrm{d}L_M}{\mathrm{d}t} &= \beta_M\frac{I_H(t)}{N_H(t)}S_M(t) - e^{-\mu_M\tau}\beta_M\frac{I_H(t-\tau)}{N_H(t-\tau)}S_M(t-\tau) - \mu_M L_M(t),\\
\frac{\mathrm{d}I_M}{\mathrm{d}t} &= e^{-\mu_M\tau}\beta_M\frac{I_H(t-\tau)}{N_H(t-\tau)}S_M(t-\tau) - \mu_M I_M(t),\\
N_M(t) &= S_M(t) + L_M(t) + I_M(t).
\end{aligned} \tag{2.4}$$

The model given by Equations (2.3) and (2.4) is a fairly simple model based on the work of the early mathematical epidemiologists MacDonald [97], Ross [127] and Kermack and McKendrick [88]. However, much more complicated compartmental models have been derived since the introduction of the Ross-MacDonald type models. Some models, for example, consider variable population sizes or environmental factors that influence the transmission dynamics [145]. Anderson and May [11] further adapted the previous models by Ross and MacDonald to include additional compartments and an age-dependence in the acquisition of infection. This age-dependence in the rate of new infections at least slightly relaxes the homogeneous mixing assumption but makes it necessary to consider partial differential equations and integro-differential equations. Independent of the type of differential equations used to model the dynamics, the two species are always modelled with a compartmental structure.

### 2.2.3 Key Concepts

Some key concepts of mathematical epidemiology can be determined for all Ross-MacDonald type models, independent of their complexity. The two most important ones are the basic reproduction number and the force of infection.

#### The Basic Reproduction Number

Ross's [127] work on malaria is considered pioneering in terms of disease control. This is due to one of the key results Ross arrived at by analysing his model, namely the existence of a threshold quantity below which malaria can be eradicated from the population. Prior to this discovery it was widely believed that for eradication of malaria the complete eradication of its vectors is necessary. Ross's result, however, indicated that reducing the number below a certain level is sufficient to prevent the spread of malaria. MacDonald [97] referred to this quantity as the basic reproduction rate.

The basic reproduction rate or basic reproduction number is typically denoted by $R_0$ and defined as 'the number of secondary cases one typical infectious individual produces during his or her entire infectious period in a completely susceptible population' [77]. The importance of the basic reproduction number for mathematical epidemiology arises from its threshold property. Usually we find that the disease will eventually die out if $R_0 < 1$, while for $R_0 > 1$ the disease will spread in the population. This quantity is therefore particularly relevant for the evaluation of control methods.

The basic reproduction number depends on the underlying assumptions of a model. However, it is often possible to intuitively derive a simple expression for $R_0$ by considering the transmission dynamics. This will be done for an age-dependent dengue transmission model later on in this thesis (cf. Section 3.2.3).

#### The Force of Infection

Another significant quantity in epidemiological modelling is the force of infection which is the per capita rate at which susceptible individuals become infected [77]. Clearly the force of infection depends on whether density-dependent or frequency-dependent transmission is assumed. Most commonly the force of infection is denoted by $\lambda(t)$. It was proposed as an important parameter by Hens et al. [77] only in 1934 despite being included, albeit implicitly, in the models of Ross and Kermack and McKendrick.

For a directly transmitted disease the force of infection based on density-dependent and frequency-dependent transmission are obtained as

$$\lambda'_H(t) = \beta'_H I_H(t) \qquad \text{and} \qquad \lambda_H(t) = \beta_H \frac{I_H(t)}{N_H(t)} \tag{2.5}$$

respectively. On the other hand, for models of vector-transmitted diseases like that presented in Equations (2.3) and (2.4) there are in fact two distinct forces of infection, the force of infection in the human population, $\lambda_H(t)$, and the force of infection in the mosquito population, $\lambda_M(t)$. They are analogously given by

$$\lambda_H(t) = \beta_H \frac{I_M(t)}{N_H(t)} \qquad \text{and} \qquad \lambda_M(t) = \beta_M \frac{I_H(t)}{N_H(t)} \tag{2.6}$$

if the mass action law is applied with a frequency-dependent transmission.

The force of infection can often be estimated more directly than the basic reproduction number [77]. If the transmission dynamics are not assumed to be age-dependent an approximation can, for example, be obtained from the average age of infection, $A$, through the relation $\lambda = 1/A$ [11]. The force of infection is also considered to be of paramount importance since knowledge about it makes it possible to estimate all other model parameters.

## 2.3 Modelling Dengue

There are a large variety of mathematical models that describe the transmission dynamics of dengue based on the classical Ross-MacDonald type model. A simple, deterministic Ross-MacDonald type model describing the human and mosquito population is often extended through additional compartments in one or both populations. Which compartments are considered for a specific model depends on the research question that is to be tackled with its help. In addition to this, Ross-MacDonald type models can be adapted to consider more complex aspects of dengue transmission. Common examples are the incorporation of a stochastic component in the transmission dynamics and the consideration of age-structure in the human population.

The different Ross-MacDonald type dengue models can, in fact, be classified according to a number of typical characteristics. Andraud et al. [12] and Johansson et al. [85], who reviewed a number of dengue models, found dengue to be more frequently modelled deterministically than stochastically so that deterministic models will be the main focus in this section. For dengue models one of

the most important distinctions is whether the model describes the transmission of a single-serotype only or explicitly models the interactions between multiple serotypes.

### 2.3.1 Single-Serotype Models

Single-serotype models do not necessarily describes a specific dengue serotype. Instead they are often used to model dengue in general without making any distinction between the different serotypes (e.g. [50, 102]). However, not all single-serotype models follow the structure of the simple model presented in Figure 2.1. There are a number of different refinements that lead to much more complex models.

One typical alteration is to represent the mosquito population in more detail [12]. Models with a higher number of mosquito compartments are typically used to evaluate the effect of vector control strategies. It is, for example, necessary to model the larval stages of the mosquito population explicitly if the aim is to determine whether larvicides can reduce the number of dengue cases. However, such models are also useful to detect the effect of environmental changes. Andraud et al. [12] identified further complexities that were introduced and studied with the help of single-serotype models. Those include, but are not limited to, the seasonality of the transmission dynamics and alternative transmission routes, e.g. vertical transmission in the mosquito population.

Erickson et al. [46] and Chen and Hsieh [36] both aimed to determine the importance of temperature on the outbreak dynamics of dengue and thus included pre-adult mosquito compartments in their models. However, the two models are widely different. Erickson et al. [46] explicitly described six life-stages of the mosquito, three pre-adult stages (eggs, larvae, pupae) and three stages of adult mosquitoes (immature, gestating, reproducing). Only blood-feeding mosquitoes, i.e. gestating and reproducing adults, were further subdivided into susceptible, exposed and infectious mosquitoes. The model by Chen and Hsieh [36], on the other hand, only extended the simple model shown in Figure 2.1 by two pre-adult mosquito compartments. These compartments did not represent different life-stages but rather separated all pre-adult mosquitoes into infected and susceptible depending on whether an egg was laid by an infectious mosquito or not. Chen and Hsieh [36] thus included vertical transmission of the virus in the mosquito population. This difference in the two models is due to the studied regions. Chen and Hsieh [36] used their model to evaluate the temperature effects in subtropical Taiwan where transovarial transmission has been observed, while Erickson et al.

[46] studied the dynamics at the border between the United States and Mexico where it is believed that the climate does not facilitate this transmission route. Despite the differences both models were able to demonstrate that temperature does indeed significantly impact the transmission of dengue.

In addition to or instead of refining the representation of the mosquito population, the human population is also sometimes subdivided further than into the number of susceptible, infected and recovered. Clearly the incorporation of vaccination can be achieved by introducing an additional compartment for vaccinated individuals. However, even if vaccination is not considered, the description of the human population can be refined. Indeed, Andraud et al. [12] found that some researchers have divided the population into different age-classes to study the age-structure of infected individuals. Commonly two age-classes are considered to differentiate between adults and younger individuals [121, 150]. This is due to dengue being considered a childhood disease, i.e. infections occur much more frequently among children than among adults. By separating the human population into juveniles and adults the differences in transmission can be incorporated and their effect studied. Modelling age-densities is also not uncommon and particularly useful for the evaluation of vaccination campaigns. Considering age-densities rather than age-classes can make the evaluation of the model more complicated. However, it also permits a much more detailed look at the effects related to age. For vaccination this is particularly important since the exact vaccination age has a large impact on the outcome of a vaccination campaign.

Another common adaptation to the simple model shown in Figure 2.1 is the differentiation between certain groups in the human population. Amaku et al. [7], for example, modelled a population by dividing it into sub-populations which each inhabit a certain district but may occasionally move between them. By doing so they were able to demonstrate the importance of movement and spatial heterogeneity. In addition they considered seasonality and were thus able to reproduce and predict dengue patterns observed in previous outbreaks. They also showed that the simple Ross-MacDonald model is able to capture some key aspects of dengue transmission, e.g. the total number of cases can be correctly predicted even without these complexities.

Instead of considering populations according to different neighbourhoods, another common differentiation is to divide the population into locals and visitors. Such models can help to determine the risk of dengue spreading to and within countries that are so far non-endemic as well as determine the risk to travellers themselves. This is an important area of research, particularly in light of the fast

mode of travel that aeroplanes provide, the large number of tourists travelling to and from endemic regions and the changing climate which creates new habitats for dengue transmitting vectors. Lopez et al. [95] and Massad et al. [100] used fairly simple single-serotype models of dengue to study the risk of virus importation. Massad et al. [100] were able to predict the risk for a number of European countries and highlighted the importance of further research. While these simple models give a first indication of the risk, Lopez et al. [95] correctly point out that deterministic models have their limits. This is especially important when considering the risk of importation, as a random introduction of a high number of infected individuals under the right conditions may lead to a much higher risk. Ximenes et al. [170] separated the human population into locals and visitors to study the risk to the travellers themselves at events that draw a large crowd of foreigners to affected areas. Specifically they used a simple model based on the one shown in Figure 2.1 to determine the number of infections to foreign visitors at the Rio Olympics in 2016 and showed that their model predicted reasonable numbers by comparing the results to data from a similar event, i.e. the World Cup hosted by Brazil two years earlier.

Massad et al. [101–103] also used the simple model which was presented earlier in this chapter to study the risk of other mosquito-borne diseases such as yellow fever spreading in dengue-infested areas or to determine important aspects of dengue transmission such as the basic reproduction number or the size of the mosquito population. Despite its simplicity it can therefore be seen how many applications this model has, particularly with some small alterations.

In general single-serotype models are easier to analyse than multi-serotype models that consider the populations in the same amount of detail. The reason for this is that they do not capture any of the cross-reactions that have been observed for the four dengue serotypes (cf. Section 1.2) and thus require the modelling of fewer compartments overall. In order to study the effect of the cross-reactions on the transmission of dengue multi-serotype models are needed.

### 2.3.2 Multi-Serotype Models

Multi-serotype models can quickly become very complicated if a large number of human and mosquito compartments is considered. The transmission of dengue is therefore frequently modelled as a directly transmitted disease, i.e. the mosquito population is not explicitly considered [12, 85]. Modelling dengue as a quasi-directly transmitted disease simplifies the analysis significantly and may be

sufficiently realistic to capture important aspects of the transmission process if the considered time-scale is short and the population of mosquitoes dense enough. Additionally in multi-serotype models the number of serotypes is often restricted to only two distinct types as it has been noted that the four serotypes demonstrate pairwise similar characteristics [12, 33]. Similarly to the assumption of the disease being quasi-directly transmitted this simplification reduces the overall number of compartments significantly and makes the model analysis much easier.

Multi-serotype models and single-serotype models often tackle similar research questions. Models describing several serotypes may therefore include any of the previously named refinements. However, the most important aspect of the transmission dynamics that these models aim to shed some light on are the possible serotype and antibody cross-reactions. The cross-reaction theories were described in detail in Section 1.2. In summary it has been observed that individuals are protected against all dengue serotypes after recovery for a short period of time, that once this cross-protection wanes ADE causes more severe dengue fever cases and that two heterologous infections confer PCI since very few individuals experience symptoms in third and fourth infections. The study of multi-serotype models has furthered the understanding of the serotype and antibody cross-reactions and provided some insight into other aspects of the dengue transmission dynamics. For example, one of the key outbreak characteristics that have been captured by these models is the multi-annual cycle in which the predominant serotype is replaced that cannot be easily captured with a single-serotype model.

Andraud et al. [12] found that the cross-reactions are usually modelled by assuming an increased or reduced transmission potential or a higher or lower susceptibility to infection. In particular a higher transmission potential and higher susceptibility to infection is associated with ADE. On the other hand, cross-protection is described by previously infected individuals transmitting the virus at a lower rate or being less susceptible to a further infection. Note that the increased risk of experiencing severe symptoms due to ADE for the infected individual is not explicitly included if these methods are used, instead the higher virulence in secondary infections is assumed to have a direct effect on the transmission dynamics. Similarly the effect of PCI is considered for the entire population, i.e. individuals who have been previously infected by two serotypes will no longer contribute to the transmission cycle at the same rate as others but the higher likelihood of mild infections for them may not be modelled explicitly.

Esteva and Vargas [47] studied a model incorporating ADE and short-term cross-immunity through different rates of infection for individuals who have ex-

perienced one prior infection with a heterologous serotype. In particular they assumed that short-term cross-immunity corresponds to a reduced rate of infection and ADE to an increased rate of infection. However, by studying the possible cross-reactions in this way they did not allow for the possibility of both ADE and short-term cross-immunity to influence the dynamics at once. A number of more complex models have been derived (c.f. [85, 109]) which incorporate both cross-reaction types in different ways. Indeed it is possible to model the effects on the infected individual due to ADE and short-term cross-immunity explicitly in addition to considering a reduced or enhanced transmission potential and susceptibility. Short-term cross-protection, for example, can be modelled by an additional compartment with a lower transmission potential and no susceptibility which individuals leave at a constant rate to become completely susceptible again. ADE can also be considered by modelling a compartment for individuals with a secondary infection with an enhanced susceptibility and transmission potential but also a higher rate of mortality to account for the more severe outcome observed for these individuals [85]. By using these approaches to include cross-reaction scenarios in a dengue model it is possible to study the effect of either one or both playing an important role. Johansson et al. [85] compared a number of dengue models which aim to improve our understanding of antibody cross-reactions and thus found that short-term cross-immunity is a driving force behind the temporal characteristics of dengue outbreaks. ADE, on the other hand, does not seem to have such a large impact. However, Nagao and Koelle [109] demonstrated that temporal patterns are reproduced most accurately by a combination of ADE and short-term clinical cross-immunity, i.e. if the cross-immunity prevents clinical symptoms but not sero-conversion. Considering these contradictory results it is clear that more research into dengue cross-reaction dynamics is still needed. Multi-serotype models will be indispensable in determining the real forces behind the observed cross-reactions.

### 2.3.3 The Effect of Vaccination

Both single-serotype and multi-serotype models have been used to analyse the effects of vaccination on the transmission dynamics of dengue or their impact on the burden the disease causes [12, 85]. The two most common ways of incorporating the effect of a vaccine are to explicitly model a vaccinated compartment or to assume that vaccinated individuals behave the same way that recovered or immune individuals do. Vaccination is often not 100% effective and immunity may in some cases wear off over a period of time. The imperfection of the vaccine

can be incorporated both in an explicitly modelled vaccinated compartment and if vaccinated individuals are included in the recovered compartment. However, waning immunity cannot easily be considered if the vaccinated individuals are not explicitly modelled.

There is still a lack of sufficient data concerning the long-term effectiveness and duration of immunity that dengue vaccines confer. However, a number of models have attempted to determine the consequences of vaccination campaigns [12, 85]. Coudeville and Garnett [37], Knipl and Moghadas [90] and Ferguson et al. [51] all used multi-serotype models to determine the effect of vaccination in different populations. Coudeville and Garnett [37] and Ferguson et al. [51] each considered models which described all four dengue serotypes, whereas Knipl and Moghadas [90] considered two serotypes only. The overall agreement that resulted from the study of dengue vaccination models is that the number of cases can generally be reduced. In fact it has been found that the effect increases with the intensity of transmission, i.e. in high-transmission settings vaccination will be most beneficial. However, in the presence of ADE vaccination has been found to potentially cause more severe dengue cases especially if the vaccine-induced immunity does not last for the entire lifetime of an individual [90, 109]. This seems to be particularly true in low-transmission settings [51]. In fact, Aguiar et al. [3] have used a Ross-MacDonald type model to show that vaccination can be harmful in seronegative recipients independent of the transmission intensity. Coudeville and Garnett [37], Knipl and Moghadas [90] and Ferguson et al. [51] did not differentiate between seronegative and seropositive recipients. However, the lower probability of vaccinating seropositives in a low-transmission setting compared to a high-transmission setting explains the reduced benefit in these settings. Even before the controversy that arose after the first dengue vaccine was introduced and after a number of researchers challenged the benefits of it, it was believed that a successful vaccine candidate must protect equally against all four serotypes in order to prevent a surge in severe dengue cases. Mathematical modelling of dengue vaccination has reinforced this belief and has even led to the reconsideration of vaccine recommendations [133].

### 2.3.4 Individual-Based Models

Not all dengue models are Ross-MacDonald type models. In recent years dengue has also sometimes been modelled using models known as individual-based models or agent-based models [82, 86, 96, 120]. The underlying idea for individual-based dengue models is in fact very similar to that of Ross-MacDonald

type models, i.e. individuals progress through different stages of infection throughout their lifetime. However, the difference is the level at which the population is modelled and thus the detail which is considered. Ross-MacDonald type models are population-level models which neglect to account for differences between the individuals of the population and thus permit the study of the overall behaviour of a population. They generally assume homogeneous mixing and need to be adapted significantly to relax this assumption. Individual-based models, on the other hand, explicitly model each individual of a population and thus make it possible to incorporate individual attributes and behaviours, as well as spatial structures. The assumption of homogeneous mixing can therefore be relaxed significantly with this type of model.

There are a number of examples of individual-based dengue models, e.g. [82, 86, 96, 120]. Two fairly recent models of this type are those derived by Lourenço and Recker [96] and Perkins et al. [120]. While similar aspects were considered for the individual-based model in both studies, the main objectives of the research were fairly different.

Lourenço and Recker [96] used an individual-based model to asses the impact of a tetravalent dengue vaccine in a setting in which all four serotypes coexist. In particular they focused on describing heterogeneities caused, for example, by the movement of humans and mosquitoes or the different frequencies with which individuals get bitten even in the same location. They found that the biological uncertainties are a key factor that determines effectiveness of the vaccine and that the assessment of dengue vaccines solely with respect to symptomatic infections may not be sufficient to determine its benefits and risks.

Perkins et al. [120] did not consider vaccination, but rather focused on the spatial-temporal dynamics of dengue in their research. Their model described the contact between humans and mosquitoes with a stochastic component, included seasonality in the mosquito population and explicitly modelled differences between certain communities within the overall population. By doing so, they show that the spatial-temporal dynamics of dengue, i.e. oscillatory behaviour and predominance of a certain serotype, are not only due to serotype cross-reactions but highly influenced by host demographic factors and vector ecologies.

### 2.3.5 Simplicity versus Accuracy

Even a very simple model can often give a good initial indication for the actual behaviour of transmission dynamics. Amaku et al. [7] demonstrated this for dengue when they compared the results obtained from a more complex model

with spatial heterogeneity and seasonal variations to those obtained from the simple model presented in Figure 2.1. While a simple model may not capture all characteristics, it is able to predict certain aspects of the transmission process fairly accurately and is easy to analyse. It is therefore not surprising that the fairly basic Ross-MacDonald type model is still widely used (sometimes with small alterations) to answer important research questions. However, in all areas of mathematical modelling it is crucial to describe a dynamical system accurately enough to capture all relevant aspects of the dynamics without making a model so complex that it can no longer be analysed. Finding a balance between simplicity and accuracy is one of the key challenges when it comes to the modelling of dengue transmission and vaccination.

The simpler a model is, the easier it is to both understand and analyse the model and its results. However, if it does not capture enough of the details of the dynamics the results will be of very limited value. On the other hand, if a model is so complex that it cannot be adequately analysed, the model itself will not be useful to answer any research questions. However, not every research question can be answered with the same model. Specific questions require a more complex model to be able to incorporate the studied aspects. It is further important to keep in mind that the more complex a model gets, the more parameters need to be determined. Some parameters may be found through experiments in the field or laboratories, while others may have to be obtained by fitting the model to previously collected data. This may therefore be a limiting factor when deriving a new, complex dengue model. In fact, the limited knowledge of specific parameters relating to the behaviour and characteristics of individuals or populations is also one of the reasons why population-based models like the Ross-MacDonald type one are still more frequently used than individual-based models. For population-based models it is sufficient to determine the overall behaviour, whereas for individual-based models the differences in behaviour and characteristics need to be known.

## 2.4 Summary

In this chapter the mathematical concepts that most modern dengue models rely on have been introduced. In particular the mass action law and its two differing interpretations were discussed. Dengue models are most commonly modelled assuming a frequency-dependent transmission with the total human population size as a normalising constant. Indeed, the law of mass action is the underlying

assumption of most compartmental models in epidemiology. It was first used for vector-transmitted diseases by Ross [127]. Due to the significant improvements of Ross's model by MacDonald [97] compartmental models of vector-borne diseases are often called Ross-MacDonald type models. One such model with three compartments each for the human and mosquito population was explained in detail. All Ross-MacDonald type models share some key concepts that are modelled or can be derived from the model equations, namely the force of infection and the basic reproduction number. Their significance in epidemiological modelling was therefore highlighted as well.

Summaries of single-serotype dengue models and multi-serotype dengue models were given which make use of the previously discussed modelling approaches. Some important research questions were briefly highlighted for both types of models. The effect of vaccination is a common and important topic of dengue research. Different approaches of modelling the possible effects in Ross-MacDonald type models were outlined. In addition to the Ross-MacDonald type models which are most commonly used to describe the transmission dynamics of dengue, the approach of individual-based dengue models was briefly introduced and two recent examples discussed. Finally, the reasons for such a wide variety of dengue transmission and dengue vaccination models were highlighted. One of the main reasons is that different research questions require a more detailed look at certain aspects of the transmission dynamics and thus a more complex model. In addition there is always a need to find a balance between accuracy and simplicity so that models and results can be analysed.

The mathematical concepts that were introduced in this chapter will now be used to derive a modelling framework with which the optimal vaccination age for dengue can be determined. In particular a single-serotype model similar to that presented in Figure 2.1 will be developed. Despite modelling dengue with a single-serotype model the serotype cross-reactions will be taken into account.

Chapter 3

# Modelling Framework

## 3.1 Introduction

This chapter will introduce the modelling framework which is used throughout Chapters 4 to 6 in a general way. Specifically a single-serotype transmission model with an age-dependent force of infection for the human population and a general age-dependent human death rate is presented, analysed and an expression for its basic reproduction number is derived. The steady-state age-densities of unaffected, infected and recovered humans are determined along with the steady-state force of infection. Subsequently the lifetime expected risk for dengue is defined based on the hospitalisation risk or the lethality due to dengue in Brazil. The definition of the lifetime expected risk is adapted from that given by Hethcote [79] for measles to allow for several coexisting serotypes and further includes the survival probability of humans to prevent overrating the high risk associated with infections at older ages. The lifetime expected risk will be used to consider a number of different cross-reaction assumptions through modifications of the risk functions. The undesirability in terms of severe dengue as associated with hospitalisation or lethality in the pre-vaccine era is obtained from data collected by SINAN. In light of recent vaccine trial results the consensus regarding the possibility of a vaccine-induced risk has changed. Initially it was believed that there is no vaccine-induced risk. However, it is now believed that a vaccine recipient can experience a higher risk during break-through dengue cases depending on their serostatus at the time of vaccination (cf. Section 1.4.3). Therefore relative risks for different infection and vaccination histories are derived and incorporated in the lifetime expected risk at the end of this chapter. The theoretical results from this chapter are finally used in Chapters 4 to 6 for slightly different model assumptions.

## 3.2 A Single-Serotype Dengue Model

In order to evaluate any vaccination strategy a mathematical model describing the transmission dynamics of dengue and the effect of vaccination must be derived. The complexity of such a model can vary significantly particularly in view of the coexistence of the four distinct dengue serotypes and the complicated cross-reactions between them as mentioned in Section 2.3. By assuming independent transmission dynamics for the four serotypes it is possible to model the dynamics for each of them using a single-serotype model. This has the advantage of making both the analytical and numerical analysis of the model easier. A single-serotype model also relies on fewer parameters than a multi-serotype model which can be favorable in the absence of sufficient serotype-specific data. However, any simplification comes at the cost of accuracy, i.e. the model is only an approximation of the real transmission dynamics. A single-serotype model can nonetheless be considered a reasonable approximation since the interactions that influence the transmission of the different serotypes such as ADE and temporary cross-immunity are mainly short-term effects. A Ross-MacDonald type model is therefore introduced describing the interactions between humans and mosquitoes for each serotype separately. The model equations for the human population describe age-densities rather than total numbers so that the effect of vaccination at different ages can be considered by modelling a three-dose vaccination schedule implicitly through matching conditions. Following the description of the model the steady-state dynamics are analysed and an expression for the basic reproduction number $R_0$ is derived.

### 3.2.1 Transmission Model with Vaccination

Dengue gets transmitted from mosquitoes to humans and vice versa. A typical way to describe such a transmission cycle is a Ross-MacDonald type model which assumes that both mosquitoes and humans progress through a series of different stages during their lifetime, such as 'susceptible', 'exposed', 'infected' and 'recovered'. The transition from one stage to the next depends on assumptions specific to each population.

In the mosquito population all mosquitoes are assumed to be initially susceptible, i.e. there is no vertical transmission. The larval stages are omitted since vaccination will have no effect on these stages and only adult mosquitoes transmit the virus. A susceptible mosquito which feeds on an infected human is exposed to the virus with probability $c$ but will only become infectious after a latency period $\tau$.

During this latency period the newly exposed mosquito cannot transmit the virus to humans, but once the latency period has passed the mosquito becomes infectious. The virus does not influence the death rate $\mu_M$ of mosquitoes and also has no effect on the biting rate $q(a)$ with which humans of age $a$ are bitten by mosquitoes. The infectious mosquito does not recover from infection but will leave the compartment once it dies. For simplicity the size of the mosquito population $N_M$ is assumed to be constant and thus the rate at which new mosquitoes are recruited into the susceptible compartment is equal to the death rate $\mu_M$. The total number of mosquitoes at time $t$, $N_M(t)$, is therefore divided into 'susceptible' $S_M(t)$, 'exposed' (or latent) $L_M(t)$ and 'infectious' $I_M(t)$ mosquitoes.

For the human population, on the other hand, the age-densities of all humans $N_H(a,t)$, 'unaffected' $U_H(a,t)$, 'infected' $I_H(a,t)$ and 'recovered' $R_H(a,t)$ are modelled instead of the total numbers in each compartment. However, note that the compartment of 'unaffected' comprises susceptible individuals as well as those protected by maternal antibodies. Assuming that all humans are born passively immune and become susceptible once the maternal antibodies in their bloodstream decline according to an age-dependent function $C(a)$, the age-densities for passively immune and for susceptible humans are $(1-C(a))\,U_H(a,t)$ and $C(a)U_H(a,t)$ respectively. Only susceptible humans who are bitten by an infectious mosquito can become infected. The transmission of the virus from the infectious mosquito to the susceptible human occurs with probability $b$. Infected humans recover at a rate $\gamma_H$ and once they are recovered can never get infected by the same serotype again. The death rate in the human population is age-dependent but does not depend on whether an individual has been infected or not; therefore it is given by $\mu_H(a)$ for all compartments. Similar to the mosquito population the size of the human population $N_H$ is assumed to remain constant, i.e. $N_H = N_H(t) = \int_0^\infty N_H(a,t)\,\mathrm{d}a$, and the birth rate in the unaffected compartment is therefore $\mu_H(a)$.

Under these assumptions the force of infection for the human population is both time and age-dependent as given by

$$\lambda_H(a,t) = bq(a)I_M(t)\frac{1}{N_H}, \tag{3.1}$$

while the force of infection for the mosquito population is time-dependent only, i.e.

$$\lambda_M(t) = c\int_0^\infty q(a)I_H(a,t)\frac{1}{N_H}\,\mathrm{d}a. \tag{3.2}$$

$\frac{1}{N_H}$ is a scaling factor corresponding to the probability of a specific human being bitten by a mosquito on which the rate of adequate contacts for transmission of the virus depends. The transmission dynamics are therefore modelled by the system of partial integro-differential equations

$$\begin{aligned}
\frac{\partial U_H}{\partial a} + \frac{\partial U_H}{\partial t} &= -\lambda_H(a,t)C(a)U_H(a,t) - \mu_H(a)U_H(a,t),\\
\frac{\partial I_H}{\partial a} + \frac{\partial I_H}{\partial t} &= \lambda_H(a,t)C(a)U_H(a,t) - (\mu_H(a)+\gamma_H)\, I_H(a,t),\\
\frac{\partial R_H}{\partial a} + \frac{\partial R_H}{\partial t} &= \gamma_H I_H(a,t) - \mu_H(a)R_H(a,t),\\
\frac{\partial N_H}{\partial a} + \frac{\partial N_H}{\partial t} &= -\mu_H(a)N_H(a,t),\\
N_H(a,t) &= U_H(a,t) + I_H(a,t) + R_H(a,t),
\end{aligned} \tag{3.3}$$

for the human population and the system of ordinary integro-differential equations

$$\begin{aligned}
\frac{\mathrm{d}S_M}{\mathrm{d}t} &= \mu_M N_M(t) - \lambda_M(t)S_M(t) - \mu_M S_M(t),\\
\frac{\mathrm{d}L_M}{\mathrm{d}t} &= \lambda_M(t)S_M(t) - e^{-\mu_M\tau}\lambda_M(t-\tau)S_M(t-\tau) - \mu_M L_M(t),\\
\frac{\mathrm{d}I_M}{\mathrm{d}t} &= e^{-\mu_M\tau}\lambda_M(t-\tau)S_M(t-\tau) - \mu_M I_M(t),\\
N_M(t) &= S_M(t) + L_M(t) + I_M(t),
\end{aligned} \tag{3.4}$$

for the mosquito population.

At time $t = 0$ the age-densities for the unaffected, infected and recovered human population are $U_{H,0}(a)$, $I_{H,0}(a)$ and $R_{H,0}(a)$ respectively and thus the total human age-density is given by $N_{H,0}(a) = U_{H,0}(a) + I_{H,0}(a) + R_{H,0}(a)$. The number of susceptible, latent and infectious mosquitoes are $S_{M,0}$, $L_{M,0}$ and $I_{M,0}$ respectively and therefore $N_{M,0} = S_{M,0} + L_{M,0} + I_{M,0}$. Note that due to the latency period we assume that $I_H(a,t) = I_{H,0}(a)$ and $S_M(t) = S_{M,0}$ for $t \in [-\tau, 0]$. Additionally, at age $a = 0$ we have that $U_H(0,t) = N_{H,0}$, $I_H(0,t) = 0$, $R_H(0,t) = 0$, and $N_H(0,t) = N_{H,0} = \frac{N_H}{L}$ where $L$ is the expected lifetime of a human which depends on the death rate $\mu_H(a)$.

So far the model does not include any vaccination effects. This can be included implicitly through matching conditions for unaffected humans for each vaccination dose rather than explicitly including a 'vaccinated' compartment. The recommended schedule for Dengvaxia is a three-dose vaccination scheme at 0, 6 and 12 months. It is therefore assumed that a fraction $V_i$ of the unaffected

Table 3.1: Model parameters together with the values used in simulations and sources where appropriate.

| Notation | Biological Meaning | Value | Source |
|---|---|---|---|
| $\mu_H(a)$ | Age-dependent death rate for the human population | | |
| $\pi_H(a)$ | Age-dependent survival probability for the human population | | |
| $L$ | Expected lifetime for humans in years based on the death rate/survival probability | $\int_0^\infty \pi_H(a)\,\mathrm{d}a$ | |
| $q(a)$ | Age-dependent rate at which humans are bitten by mosquitoes | | |
| $b$ | Transmission probability from infected mosquito to susceptible human | 0.6 | [102] |
| $c$ | Transmission probability from infected human to susceptible mosquito | 1.0 | [102] |
| $\gamma_H$ | Per capita recovery rate of humans | $51.135\,\mathrm{year}^{-1}$ | [102] |
| $\mu_M$ | Natural per capita death rate of mosquitoes | $9.131\,\mathrm{year}^{-1}$ | [102] |
| $\tau$ | Extrinsic incubation period | 0.0192 years | [102] |
| $N_H$ | Total number of humans | | |
| $N_M$ | Total number of mosquitoes | | |
| $m$ | Number of mosquitoes per human | 1.5 | [50] |
| $\epsilon_j$ | Vaccine efficacy for serotype $j$ ($j = 1, 2, 3, 4$) | cf. Table 1.1 | |
| $\delta_j(a)$ | Age-dependent rate of loss of maternal antibodies for serotype $j$ | | [119] |
| $C_j(a)$ | Age-dependent rate of seroconversion/loss of maternal antibodies for serotype $j$ | $1 - e^{-\int_0^a \delta_j(s)\,\mathrm{d}s}$ | [79] |
| $A_i$ | Vaccination age for each of the three vaccination doses $i = 1, 2, 3$ | $0 - L$ years | |
| $V_i^j$ | Proportion successfully vaccinated against serotype $j$ for vaccination dose $i$ | $1 - (1 - \epsilon_j)^{1/3}$ | |
| $p_i^j$ | Probability of being successfully vaccinated against serotype $j$ at age $A_i$ | $V_i C_j(A_i)$ | |

population is vaccinated at age $A_i$ months where $i = 1, 2, 3$ and $A_2 = A_1 + 6$ months and $A_3 = A_1 + 12$ months. Similarly to Hethcote [79] the seroconversion rate is taken to be given by the same function as the loss of maternal antibodies. This leads to the probability $p_i = V_i C(A_i)$ of becoming immune due to vaccination at the vaccination age $A_i$ and the probability $1 - p_i$ of remaining unaffected, so that the matching condition resulting from vaccination at age $A_i$ is given by

$$\lim_{a \to A_i^+} U_H(a,t) = (1 - p_i) \lim_{a \to A_i^-} U_H(a,t). \tag{3.5}$$

The system of differential equations given in Equations (3.3) and (3.4) together with the matching conditions arising from vaccination can now be used to describe the transmission dynamics for any serotype. The parameters used in the model are summarised in Table 3.1 where it is also made apparent which of the model parameters are serotype-specific and which are serotype-independent.

### 3.2.2 Steady-State Dynamics

Assume that the model described in Equations (3.3) to (3.5) has reached its steady-state. The dynamics in this case will no longer be time-dependent and the steady-state age-distribution of unaffected, infected and recovered humans $U(a)$, $I(a)$ and $R(a)$ (where for example $U(a) = \lim_{t\to\infty} U_H(a,t)$) can be derived from the model equations by setting the time derivatives to zero. Once the steady-state age-distributions of the human population are known it is possible to determine the steady-state force of infection $\lambda(a)$ by noting $\lambda(a) = \lim_{t\to\infty} \lambda_H(a,t)$ and using Equation (3.1). The subscript $H$ is dropped in these definitions since only the age-distributions and the force of infection of the human population are considered.

#### Steady-State Age-Distribution of the Human Population

Denote the steady-state fraction of unaffected, infected and recovered humans of age $a$ by $u(a)$, $i(a)$ and $r(a)$ respectively, e.g. $u(a) = \frac{U(a)}{N(a)}$ where

$$\begin{aligned} N(a) &= \lim_{t\to\infty} N_H(a,t), \\ &= N(0)\pi_H(a), \\ &= \frac{N_H}{L}\pi_H(a), \end{aligned} \tag{3.6}$$

is the age-distribution of the entire human population and can easily be obtained from the equation for $N_H(a,t)$ in Equation (3.3). $u(a)$ can be understood as the

probability of a human being unaffected at age $a$ and similarly for $i(a)$ and $r(a)$. It is sufficient to consider

$$\begin{aligned} \frac{\mathrm{d}u}{\mathrm{d}a} &= -\lambda(a)C(a)u(a), \\ \frac{\mathrm{d}i}{\mathrm{d}a} &= \lambda(a)C(a)u(a) - \gamma_H i(a), \end{aligned} \tag{3.7}$$

with initial conditions $u(0) = 1$ and $i(0) = 0$, and with the matching condition

$$\lim_{a \to A_i^+} u(a) = (1 - p_i) \lim_{a \to A_i^-} u(a) \tag{3.8}$$

for vaccination at age $A_i$ for $i = 1, 2, 3$.

This system of ordinary differential equations can be solved analytically to obtain the steady-state fractions of unaffected and infected as

$$u(a) = \begin{cases} e^{-\int_0^a \lambda(s)C(s)\,\mathrm{d}s}, & 0 \le a \le A_1, \\ (1-p_1)\, e^{-\int_0^a \lambda(s)C(s)\,\mathrm{d}s}, & A_1 < a \le A_2, \\ (1-p_1)\,(1-p_2)\, e^{-\int_0^a \lambda(s)C(s)\,\mathrm{d}s}, & A_2 < a \le A_3, \\ (1-p_1)\,(1-p_2)\,(1-p_3)\, e^{-\int_0^a \lambda(s)C(s)\,\mathrm{d}s}, & A_3 < a < \infty, \end{cases} \tag{3.9}$$

and

$$i(a) = e^{-\gamma_H a} \int_0^a \lambda(s)C(s)u(s)e^{\gamma_H s}\,\mathrm{d}s. \tag{3.10}$$

Consequently $r(a) = 1 - (u(a) + i(a))$ and the steady-state age-distributions of unaffected, infected and recovered humans are $U(a) = u(a)N(a)$, $I(a) = i(a)N(a)$ and $R(a) = r(a)N(a)$ respectively.

There is no explicitly modelled population compartment for vaccinated individuals, instead a successful vaccination is considered to be a silent natural infection and successfully vaccinated individuals are therefore included in the recovered compartment. However, from the matching conditions of $u(a)$ the steady-state fraction of the population of age $a$ who was successfully vaccinated can still be obtained as

$$v(a) = \begin{cases} 0, & 0 \le a \le A_1, \\ p_1 u(A_1^-), & A_1 < a \le A_2, \\ p_1 u(A_1^-) + p_2 u(A_2^-), & A_2 < a \le A_3, \\ p_1 u(A_1^-) + p_2 u(A_2^-) + p_3 u(A_3^-), & A_3 < a < \infty, \end{cases} \tag{3.11}$$

where $u(A_i^-) = \lim_{a \to A_i^-} u(a)$. $v(a)$ thus corresponds to the probability of having been successfully vaccinated before age $a$. Being able to identify this probability makes it possible to distinguish between recovered and vaccinated individuals which is relevant when considering an increased risk in seronegative vaccine recipients.

### Steady-State Force of Infection for the Human Population

In order to derive the steady-state force of infection for the human population from Equation (3.1) the steady-state number of infectious mosquitoes needs to be known. Similar to the age-distributions of the human population the number of mosquitoes in each compartment at the steady-state can be found analytically by setting the time derivatives to zero, i.e. from the equation for $S_M(t)$ in Equation (3.4)

$$L_M^s + I_M^s = \frac{1}{\mu_M} \lambda_M^s S_M^s, \tag{3.12}$$

$$= \frac{1}{\mu_M} \lambda_M^s \left( N_M^s - (L_M^s + I_M^s) \right), \tag{3.13}$$

where $S_M^s$, $L_M^s$, $I_M^s$ and $N_M^s$ denote the steady-state numbers of susceptible, latent, infectious and all mosquitoes and $\lambda_M^s = c \int_0^\infty q(a) \frac{I(a)}{N_H} \, \mathrm{d}a$ the force of infection for mosquitoes. Hence

$$L_M^s + I_M^s = \frac{\lambda_M^s N_M^s}{\lambda_M^s + \mu_M}. \tag{3.14}$$

From the equation for $I_M(t)$ further

$$\begin{aligned} I_M^s &= e^{-\mu_M \tau} \frac{\lambda_M^s}{\mu_M} S_M^s, \\ &= e^{-\mu_M \tau} \left( L_M^s + I_M^s \right), \\ &= e^{-\mu_M \tau} \frac{\lambda_M^s N_M^s}{\lambda_M^s + \mu_M}, \\ &= e^{-\mu_M \tau} N_M^s c \frac{\int_0^\infty q(a) \frac{I(a)}{N_H} \, \mathrm{d}a}{c \int_0^\infty q(a) \frac{I(a)}{N_H} \, \mathrm{d}a + \mu_M}. \end{aligned}$$

By substituting this expression along with $I(a) = i(a)N(a)$ into Equation (3.1) one obtains the steady-state force of infection

$$\lambda(a) = q(a) \frac{mbc}{\mu_M L} e^{-\mu_M \tau} \frac{\int_0^\infty q(a) i(a) \pi_H(a) \, \mathrm{d}a}{1 + \frac{c}{\mu_M L} \int_0^\infty q(a) i(a) \pi_H(a) \, \mathrm{d}a} \tag{3.15}$$

for the human population which will later be used to determine the optimal vaccination age.

### 3.2.3 The Basic Reproduction Number

The basic reproduction number $R_0$ is one of the most important concepts in mathematical epidemiology as it can provide an indication about whether an infection will spread in a population or not. Namely, if $R_0 < 1$ the disease dies out and if $R_0 > 1$ the disease causes an epidemic. This becomes apparent as $R_0$ is defined as the number of secondary infections caused by the average infected individual in an otherwise entirely susceptible population at equilibrium, i.e. if each infected individual infects more than one person then we expect that the disease spreads. The basic reproduction number for the model given in Equations (3.3) and (3.4) can be derived intuitively based on this definition following, for example, the approach of Massad et al. [102] for their dengue model. Additionally it is possible to approximate the basic reproduction number by linearisation and to then obtain estimates from the initial phase of an outbreak [50, 102, 103].

#### Intuitive Expression for the Basic Reproduction Number

Consider an infected individual of age $a$ who enters a completely naive population, i.e. a population where everyone else is unaffected and all mosquitoes are susceptible. This infected individual will cause a certain age-distribution of newly infected humans $f(a, a')$ which depends on the number of mosquitoes that become infectious due to the infected individual and the age-distribution of humans infected by one of those mosquitoes. Denote the number of infectious mosquitoes caused by the single infected individual of age $a$ by $T_{H\to M}(a)$ and the age-distribution of infected humans caused by one of the resulting infectious mosquitoes by $T_{M\to H}(a')$ then

$$f(a, a') = T_{H\to M}(a)T_{M\to H}(a'). \tag{3.16}$$

The initially infected individual is still infectious and alive at age $s > a$ with probability $e^{-\int_a^s (\mu_H(s')+\gamma_H)\,\mathrm{d}s'} = \frac{\pi_H(s)}{\pi_H(a)}e^{-\gamma_H(s-a)}$, so that the total cumulative contribution of the infected individual to the force of infection for the mosquito population is $c\int_a^\infty q(s)e^{-\gamma_H(s-a)}\frac{\pi_H(s)}{\pi_H(a)N_H}\,\mathrm{d}s$. There are $N_M$ mosquitoes in the population which may be exposed to dengue by biting the infected human and the probability that an exposed mosquito becomes infectious is $e^{-\mu_M\tau}$. Let $m = \frac{N_M}{N_H}$,

then the number of infectious mosquitoes is obtained as

$$T_{H\to M}(a) = mce^{-\mu_M\tau}\int_a^\infty q(s)\frac{\pi_H(s)}{\pi_H(a)}e^{-\gamma_H(s-a)}\,\mathrm{d}s. \tag{3.17}$$

On the other hand, an infectious mosquito remains infectious, i.e. alive, for a period $\frac{1}{\mu_M}$ resulting in the total cumulative contribution to the force of infection for the human population $bq(a')\frac{1}{\mu_M N_H}$. A mosquito can infect any susceptible human with the age-density of susceptible humans being given by $C(a')u(a')$. It is assumed that apart from a single individual all humans are unaffected so that $u(a') = \pi_H(a')\frac{N_H}{L}$ and therefore

$$T_{M\to H}(a') = \frac{b}{\mu_M L}q(a')C(a')\pi_H(a'). \tag{3.18}$$

The age-distribution $f(a, a')$ of newly infected humans caused by a single infected of age $a$ can therefore be factorised as a function of $a$ multiplied by a function of $a'$. Hence the basic reproduction number $R_0$ is obtained as the largest eigenvalue of $f(a, a')$ which is given by its trace [41], i.e.

$$\begin{aligned} R_0 &= \int_0^\infty f(a,a)\,\mathrm{d}a \\ &= \frac{mbce^{-\mu_M\tau}}{\mu_M L}\int_0^\infty q(a)C(a)\int_a^\infty q(s)\pi_H(s)e^{-\gamma_H(s-a)}\,\mathrm{d}s\,\mathrm{d}a. \end{aligned} \tag{3.19}$$

$R_0$ can similarly be defined as the expected number of secondary infected mosquitoes caused by a single infectious mosquito entering a completely naive population at equilibrium. This derivation results in the same expression for $R_0$. It is indeed a simpler approach as a single number rather than the spectral radius of an operator is obtained.

### Practical Calculation of the Basic Reproduction Number

Using Equation (3.19) to determine the serotype-specific basic reproduction numbers is difficult since some of the parameters, for example the disease transmission probabilities $b$ and $c$, are difficult to estimate for each serotype. However, it is relatively easy to estimate the initial growth rate of an epidemic from data. Hence an alternative expression of $R_0$ will be derived using parameters which are easy to estimate rather than difficult to estimate parameters such as $b$ and $c$.

In order to derive an expression of the basic reproduction number that relies on easily obtainable parameters the model equations for infected humans and infectious mosquitoes can be linearised. Denote the densities with respect to

age of the proportions of the human population who are unaffected humans of age $a$ and infected humans of age $a$ by $u_H(a,t) = \frac{U_H(a,t)}{N_H}$ and $i_H(a,t) = \frac{I_H(a,t)}{N_H}$ respectively. Also denote the proportions of susceptible mosquitoes and infectious mosquitoes at time $t$ by $s_M(t) = \frac{S_M(t)}{N_M}$ and $i_M(t) = \frac{I_M(t)}{N_M}$ respectively. Consider the beginning of an epidemic, i.e. $u_H(a,t) \simeq \frac{1}{L}\pi_H(a)$ and $s_M(t-\tau) \simeq s_M(t) \simeq 1$. Then the linearised system is

$$\begin{aligned} \frac{\partial i_H}{\partial a} + \frac{\partial i_H}{\partial t} &= \frac{mb}{L} q(a) C(a) i_M(t) \pi_H(a) - (\mu_H(a) + \gamma_H)\, i_H(a,t), \\ \frac{\mathrm{d}i_M}{\mathrm{d}t} &= e^{-\mu_M \tau} c \int_0^\infty q(a) i_H(a, t-\tau)\, \mathrm{d}a - \mu_M i_M(t), \end{aligned} \tag{3.20}$$

which can easily be solved by substituting $i_H(a,t) = c_H(a)e^{\alpha t}$ and $i_M(t) = c_M e^{\alpha t}$ to obtain

$$\frac{mbce^{-\mu_M \tau}}{L} = (\alpha + \mu_M)\, e^{\alpha\tau} \left[ \int_0^\infty q(a)\pi_H(a) \int_0^a q(s) C(s) e^{-(\alpha+\gamma_H)(a-s)}\, \mathrm{d}s\, \mathrm{d}a \right]^{-1}. \tag{3.21}$$

$\alpha$ is the growth rate of the epidemic during the initial exponential increase in the number of cases. The alternative expression for the basic reproduction number is

$$R_0 = e^{\alpha\tau} \frac{\alpha + \mu_M}{\mu_M} \frac{\int_0^\infty q(a)C(a) \int_a^\infty q(s)\pi_H(s) e^{-\gamma_H(s-a)}\, \mathrm{d}s\, \mathrm{d}a}{\int_0^\infty q(a)\pi_H(a) \int_0^a q(s) C(s) e^{-(\alpha+\gamma_H)(a-s)}\, \mathrm{d}s\, \mathrm{d}a} \tag{3.22}$$

which can be further simplified by approximating $C(a) \equiv 1$.

An estimate for the basic reproduction number can now be found by using case report data to identify the initial exponential growth rate $\alpha$ at the beginning of an epidemic. This approach has been used to determine the basic reproduction number for dengue previously [50, 102, 103] and will be used in this thesis in Chapters 4 and 5.

## 3.3 The Risk of Dengue

The model that was derived and analysed in the last section could in theory be used by itself to find the optimal vaccination age with respect to the lowest number of infected humans at the steady-state. However, many dengue infections are asymptomatic or very mild and it is assumed that secondary infections, which occur less frequently, are more risky. Defining the optimal vaccination age in terms of the minimal number of infections might therefore not reduce the burden of dengue on the society significantly as it is possible that mainly asymptomatic

infections would be prevented if this definition was considered. For dengue the optimal vaccination age therefore needs to be defined in a different way. One option is to define it in terms of the risk an average individual is exposed to during their lifespan, i.e. in terms of the lifetime expected risk, as was done for measles by Hethcote [79]. The risk can be understood as some measure of the undesirability of an infection where in the case of dengue any adverse events caused by an infection could be considered.

In this section the lifetime expected risk for the previously derived vaccination model is introduced by first considering the expected risk due to infection with a specific serotype at age $a$. Based on this expected risk Hethcote's [79] definition of the lifetime expected risk is then adapted to allow for several coexisting serotypes. The survival probability, which was neglected by Hethcote, will also be included in the lifetime expected risk. Including this probability is important because dengue can be contracted by individuals of any age even though it is often considered a childhood disease. In fact, the risk associated with infections at older ages is very high in comparison to the risk for young adults or middle-aged people. This increased risk should not be disregarded but it should also not be overrated which is why the survival probability needs to be included in the lifetime expected risk. Once the undesirability of an infection is defined based on hospitalisation and lethality data that was collected by SINAN the importance of the survival probability becomes apparent. Additionally the risk of an infection has recently been found to depend on the infection and vaccination history of an individual, i.e. there is the potential for vaccine-induced risk if a seronegative individual is successfully vaccinated. This vaccine-induced risk will only be considered for the risk of hospitalisation since no data for potential changes in the mortality rates due to catching dengue after being successfully vaccinated against another serotype are currently available.

### 3.3.1 The Lifetime Expected Risk

Assume that the vaccination model described in Section 3.2.1 has reached its steady-state. The model reflects the transmission dynamics of one of the serotypes so that subscripts are used to differentiate between the different serotypes. The probabilities of being unaffected by, having been successfully vaccinated against or having had an infection with serotype $i$ at age $a$ are therefore given by $u_i(a)$, $v_i(a)$ and $1-(u_i(a)+v_i(a))$ respectively. Additionally the fraction of unaffected who seroconvert upon exposure to serotype $i$ at age $a$ is $C_i(a)u_i(a)$ and the force of infection is $\lambda_i(a)$ so that the probability of infection with serotype $i$ at age $a$

is given by $P_i(a) = \lambda_i(a)C_i(a)u_i(a)$. The expected risk from serotype $i$ at age $a$ can be obtained as

$$E_i(a) = P_i(a)R_i(a) = \lambda_i(a)C_i(a)u_i(a)R_i(a) \tag{3.23}$$

where the risk of an infection with serotype $i$ at age $a$ is denoted by $R_i(a)$.

An infection with serotype $i$ can, however, be a primary, secondary, tertiary or quaternary infection which have different risks associated with them. The expected risk therefore needs to take account of this. The probabilities for the different types of infections depend on whether an individual was previously vaccinated or infected with any of the remaining serotypes, i.e. their infection and vaccination history. Let the subscripts

- $j$ indicate a natural infection with serotype $j$ before age $a$,
- $j_*$ indicate a successful vaccination against serotype $j$ before age $a$, and
- $\bar{j}$ indicate the absence of any antibodies specific to serotype $j$ at age $a$, i.e. no previous infection or successful vaccination.

The probabilities of an infection with serotype $i$ at age $a$ for any combination of previous infections and successful immunisations are then given by

$$\begin{aligned}
P_{i\bar{j}\bar{k}\bar{l}}(a) &= \lambda_i(a)C_i(a)u_i(a)u_j(a)u_k(a)u_l(a),\\
P_{ij\bar{k}\bar{l}}(a) &= \lambda_i(a)C_i(a)u_i(a)\left(1-(u_j(a)+v_j(a))\right)u_k(a)u_l(a),\\
P_{ij_*\bar{k}\bar{l}}(a) &= \lambda_i(a)C_i(a)u_i(a)v_j(a)u_k(a)u_l(a),\\
P_{ijk\bar{l}}(a) &= \lambda_i(a)C_i(a)u_i(a)\left(1-(u_j(a)+v_j(a))\right)\left(1-(u_k(a)+v_k(a))\right)u_l(a),\\
P_{ijk_*\bar{l}}(a) &= \lambda_i(a)C_i(a)u_i(a)\left(1-(u_j(a)+v_j(a))\right)v_k(a)u_l(a),\\
P_{ij_*k_*\bar{l}}(a) &= \lambda_i(a)C_i(a)u_i(a)v_j(a)v_k(a)u_l(a),\\
P_{ijkl}(a) &= \lambda_i(a)C_i(a)u_i(a)\left(1-(u_j(a)+v_j(a))\right)\\
&\qquad \left(1-(u_k(a)+v_k(a))\right)\left(1-(u_l(a)+v_l(a))\right),\\
P_{ijkl_*}(a) &= \lambda_i(a)C_i(a)u_i(a)\left(1-(u_j(a)+v_j(a))\right)\left(1-(u_k(a)+v_k(a))\right)v_l(a),\\
P_{ijk_*l_*}(a) &= \lambda_i(a)C_i(a)u_i(a)\left(1-(u_j(a)+v_j(a))\right)v_k(a)v_l(a),\\
P_{ij_*k_*l_*}(a) &= \lambda_i(a)C_i(a)u_i(a)v_j(a)v_k(a)v_l(a).
\end{aligned} \tag{3.24}$$

Here seropositivity due to infection and vaccination are treated separately but it is also possible to not make any distinction between antibodies due to a natural infection or due to successful vaccination. In this case let the subscripts

- $j_+$ indicate antibodies due to natural infection with or vaccination against serotype $j$ before age $a$, and
- $\bar{j}$ indicate the absence of any antibodies specific to serotype $j$ at age $a$, i.e. no previous infection or successful vaccination.

The likelihood of an infection with serotype $i$ at age $a$ being a primary, secondary, tertiary or quaternary infection can be calculated from the probabilities in Equation (3.24), e.g. for a quaternary infection it is

$$\begin{aligned} P_{ij_+k_+l_+}(a) = {} & P_{ijkl}(a) + P_{ij_*kl}(a) + P_{ijk_*l}(a) + P_{ijkl_*}(a) \\ & + P_{ij_*k_*l}(a) + P_{ij_*kl_*}(a) + P_{ijk_*l_*}(a) + P_{ij_*k_*l_*}(a). \end{aligned}$$

However, it is easier to compute the probabilities of an infection being a primary, secondary, tertiary or quaternary infection from the fraction of unaffected $u_i(a)$ as

$$\begin{aligned} P_{i\bar{j}\bar{k}\bar{l}}(a) &= \lambda_i(a)C_i(a)u_i(a)u_j(a)u_k(a)u_l(a), \\ P_{ij_+\bar{k}\bar{l}}(a) &= \lambda_i(a)C_i(a)u_i(a)(1-u_j(a))u_k(a)u_l(a), \\ P_{ij_+k_+\bar{l}}(a) &= \lambda_i(a)C_i(a)u_i(a)(1-u_j(a))(1-u_k(a))u_l(a), \\ P_{ij_+k_+l_+}(a) &= \lambda_i(a)C_i(a)u_i(a)(1-u_j(a))(1-u_k(a))(1-u_l(a)). \end{aligned} \tag{3.25}$$

In both cases the associated risk with any infection and vaccination history is denoted similarly to the corresponding probability, e.g. $R_{i\bar{j}\bar{k}\bar{l}}(a)$ is the risk associated with an infection with serotype $i$ at age $a$ when an individual has had no previous infection with or successful vaccination against any other serotype. Then the expected risk at age $a$ in the case of differentiating between vaccine-induced and naturally acquired antibodies is

$$\begin{aligned} E_i(a) = {} & P_{i\bar{j}\bar{k}\bar{l}}(a)R_{i\bar{j}\bar{k}\bar{l}}(a) + P_{ij\bar{k}\bar{l}}(a)R_{ij\bar{k}\bar{l}}(a) + P_{i\bar{j}k\bar{l}}(a)R_{i\bar{j}k\bar{l}}(a) \\ & + P_{i\bar{j}\bar{k}l}(a)R_{i\bar{j}\bar{k}l}(a) + P_{ij_*\bar{k}\bar{l}}(a)R_{ij_*\bar{k}\bar{l}}(a) + P_{i\bar{j}k_*\bar{l}}(a)R_{i\bar{j}k_*\bar{l}}(a) \\ & + P_{i\bar{j}\bar{k}l_*}(a)R_{i\bar{j}\bar{k}l_*}(a) + P_{ijk\bar{l}}(a)R_{ijk\bar{l}}(a) + P_{ij\bar{k}l}(a)R_{ij\bar{k}l}(a) \\ & + P_{i\bar{j}kl}(a)R_{i\bar{j}kl}(a) + P_{ij_*k_*\bar{l}}(a)R_{ij_*k_*\bar{l}}(a) + P_{ij_*\bar{k}l_*}(a)R_{ij_*\bar{k}l_*}(a) \\ & + P_{i\bar{j}k_*l_*}(a)R_{i\bar{j}k_*l_*}(a) + P_{ijk_*\bar{l}}(a)R_{ijk_*\bar{l}}(a) + P_{ij\bar{k}l_*}(a)R_{ij\bar{k}l_*}(a) \\ & + P_{ij_*k\bar{l}}(a)R_{ij_*k\bar{l}}(a) + P_{ij_*\bar{k}l}(a)R_{ij_*\bar{k}l}(a) + P_{i\bar{j}kl_*}(a)R_{i\bar{j}kl_*}(a) \\ & + P_{i\bar{j}k_*l}(a)R_{i\bar{j}k_*l}(a) + P_{ijkl}(a)R_{ijkl}(a) + P_{ijkl_*}(a)R_{ijkl_*}(a) \\ & + P_{ijk_*l}(a)R_{ijk_*l}(a) + P_{ij_*kl}(a)R_{ij_*kl}(a) + P_{ijk_*l_*}(a)R_{ijk_*l_*}(a) \\ & + P_{ij_*kl_*}(a)R_{ij_*kl_*}(a) + P_{ij_*k_*l}(a)R_{ij_*k_*l}(a) + P_{ij_*k_*l_*}(a)R_{ij_*k_*l_*}(a), \end{aligned} \tag{3.26}$$

and if there is no difference between vaccine-induced and naturally acquired antibodies it is

$$\begin{aligned} E_i(a) = {} & P_{i\bar{j}\bar{k}\bar{l}}(a)R_{i\bar{j}\bar{k}\bar{l}}(a) + P_{ij_+\bar{k}\bar{l}}(a)R_{ij_+\bar{k}\bar{l}}(a) \\ & + P_{i\bar{j}k_+\bar{l}}(a)R_{i\bar{j}k_+\bar{l}}(a) + P_{i\bar{j}\bar{k}l_+}(a)R_{i\bar{j}\bar{k}l_+}(a) \\ & + P_{i\bar{j}k_+l_+}(a)R_{i\bar{j}k_+l_+}(a) + P_{ij_+\bar{k}l_+}(a)R_{ij_+\bar{k}l_+}(a) \\ & + P_{ij_+k_+\bar{l}}(a)R_{ij_+k_+\bar{l}}(a) + P_{ij_+k_+l_+}(a)R_{ij_+k_+l_+}(a). \end{aligned} \tag{3.27}$$

Once the expected risk from an infection with a specific serotype at age $a$ is known the lifetime expected risk can be defined as

$$E = \int_0^\infty \pi_H(a) \sum_{i=1}^{4} E_i(a)\,\mathrm{d}a \tag{3.28}$$

which allows for the coexistence of several serotypes and includes the survival probability $\pi_H(a)$. Note that if serotype $i$ is not present $\lambda_i(a)$ is zero so that the expected risk due to this serotype is zero and there is no contribution to the lifetime expected risk.

To compute the lifetime expected risk it is necessary to measure the undesirability of an infection with dengue which will be done in the following subsection.

### 3.3.2 Undesirability of an Infection

The lifetime expected risk is defined in terms of some measurable undesirability of an infection. Dengue infections are often asymptomatic and even if an infected individual experiences symptoms the diagnosis of dengue can be difficult as many of the symptoms, particularly during the early stages of the infection, are very similar to those of other diseases. Even though the number of infections could be derived from the model it is therefore not the best choice to consider the risk in terms of infections themselves. Instead it may be better to define it based on the risk of experiencing severe dengue, i.e. what was previously known as DHF or DSS. The difficulty is that the model cannot predict the number of severe dengue cases and case report data is not necessarily limited to severe dengue but also includes milder cases. However, SINAN records all reported dengue cases together with their outcome in Brazil which enabled Burattini et al. [29, 30] to evaluate the age-dependence of the risk of requiring hospitalisation due to dengue and lethality from data collected between 2000 and 2014. These risks can naturally be considered to be closely related to the risk of severe dengue. According to the results of Burattini et al. the age-dependent risks of hospitalisation $R^H(a)$ and of lethality $R^L(a)$ are determined below.

### Hospitalisation

Hospitalisation is required in roughly 8% of dengue cases overall in Brazil [29]. However, the risk of being hospitalised varies significantly with age. Children below the age of 10 years experience the highest risk of being admitted when they contract the disease. They are being hospitalised at approximately twice the average rate. For young adults between the ages of 21 and 35 years the risk is lowest at 5.64%. As with many diseases an infection at older ages results in a higher risk compared to that of middle-aged individuals which is possibly due to overall poorer health in this age-group. In Brazil the risk starts to significantly increase for ages above 65 years. Based on these observations the function $R^H(a)$ describing the risk of being hospitalised due to dengue in Brazil was fitted as a continuous, piecewise defined function as shown in Figure 3.1.

It was assumed that the initial peak at approximately 5.5 years is reached due to a function of type $l_1 a e^{l_2 a}$ describing the risk at younger ages and the increasing risk in the adult population is described by an exponential function. For ages above the maximum recorded age the risk is assumed to remain constant. The age from which the risk can be described by an exponential function was fitted as an additional parameter and obtained as 21.33 years which is very close to the age at which the lowest risk was recorded (21 years). The resulting risk function for the risk of hospitalisation due to dengue in Brazil is shown alongside the data

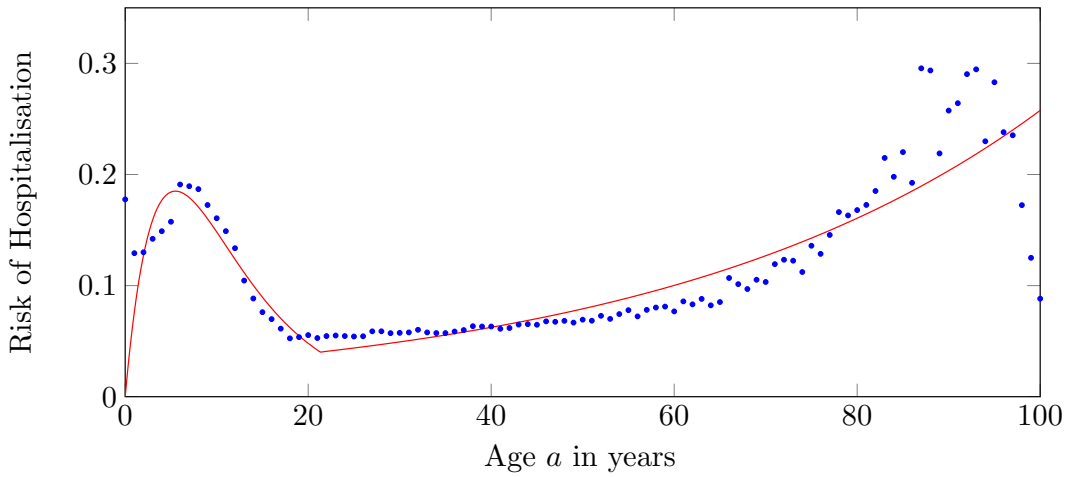



Figure 3.1: The age-dependent probability of requiring hospital treatment for a dengue infection recorded for ages between 0 and 100 years (blue dots) as evaluated from SINAN data by Burattini et al. [29, 30]. The risk function $R^H(a)$ (red line) was fitted using a piecewise defined function and is given by Equation (3.29).

in Figure 3.1 and given by

$$R^H(a) = \begin{cases} 0.09153ae^{-0.1820a}, & 0 \leq a < 21.33, \\ 0.02428e^{0.02362a}, & 21.33 \leq a < 100, \\ 0.02428e^{2.36200}, & 100 \leq a < \infty. \end{cases} \tag{3.29}$$

At extremely large ages (95–100 years) the risk of hospitalisation according to the data actually goes down as can be seen in Figure 3.1. This might be because a large percentage of individuals at these extremely large ages are resident in nursing homes prior to catching dengue and so are treated there. At these extremely large ages, the fitted curve does not fit the data particularly well, but since the proportion of individuals surviving at such large ages is extremely small this will not make a significant difference to the results.

### Lethality

It is reasonable to assume that the vast majority of dengue cases with a fatal outcome are unsuccessfully treated in hospital prior to the death of the patient. Accordingly the risk of hospitalisation and lethality can be expected to be closely related with the risk of lethality being much lower. The data for deaths due to dengue in Brazil which was collected by SINAN and evaluated for age-differences by Burattini and Massad [30] shows that the risk of dying due to an infection with dengue is in fact much lower than that of being admitted to hospital. For children below the age of 10 years the risk of an infection being fatal is high, but the highest lethality is reached at approximately 4 years which is slightly before the age at which the risk of hospitalisation is highest. As with hospitalisation the risk is low for young adults and middle-aged individuals but increases in the older age-groups. However, the risk of lethality increases drastically above the age of 60 years and is much higher for older individuals than for children. This is certainly due to underlying health issues at old age. The function describing the risk of lethality due to dengue in Brazil was obtained similarly to the risk of hospitalisation by fitting a continuous, piecewise defined function to the corresponding data as shown in Figure 3.2 and is given by

$$R^L(a) = \begin{cases} 6.95236 \times 10^{-4} ae^{-0.232273a}, & 0 \leq a < 20.33, \\ 3.26903 \times 10^{-5} e^{0.0662235a}, & 20.33 \leq a < 100, \\ 3.26903 \times 10^{-5} e^{6.6223500}, & 100 \leq a < \infty. \end{cases} \tag{3.30}$$

By comparing Figures 3.1 and 3.2 it can be seen that the risk of lethality is much lower overall than the risk of hospitalisation as one would expect. Additionally it becomes apparent that the two risk functions indeed have a qualitatively similar shape with respect to higher risks at young ages and an increasing risk for older individuals. However, this increase is much more drastic for the risk of lethality. In both cases it is essential to consider the survival probability in the computation of the lifetime expected risk so as not to overrate this high risk in comparison to the risk young children experience.

The risk functions defined in the previous subsection can now be related to either the risk of hospitalisation or the risk of lethality and it is even possible to incorporate the effect of serotype cross-reactions in the lifetime expected risk. This can be done by adapting these risks depending on the different assumptions relating to ADE and PCI as will be described in detail in the following sections.

## 3.4 Cross-Reaction Scenarios

Dengue is considered the most important viral disease transmitted by mosquitoes and yet many of its characteristics are still not fully explored and understood [165]. ADE is one theory that has been used to explain the higher disease severity in individuals with prior infections as early as the 1970s [67]. This phenomenon has been shown in vitro and in animal models but has only recently been demon-

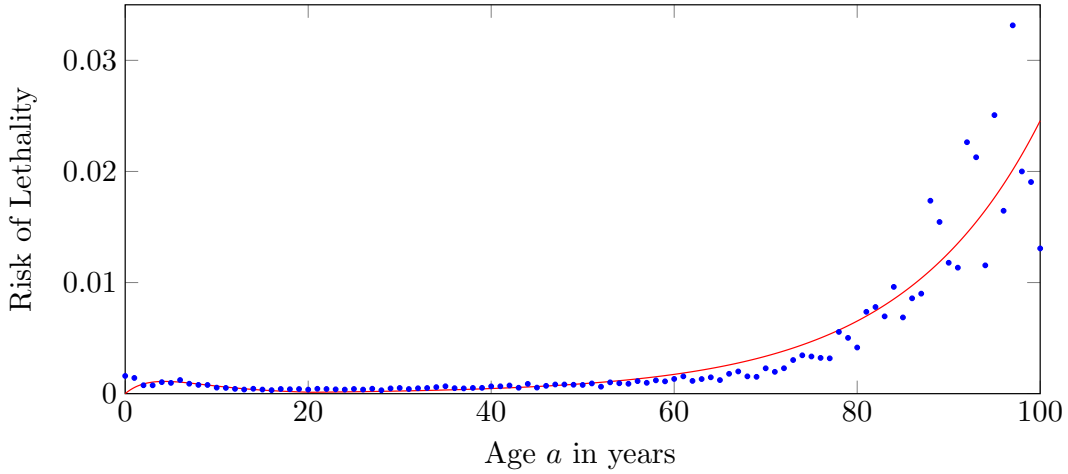



Figure 3.2: The age-dependent probability of dying due to a dengue infection recorded for ages between 0 and 100 years (blue dots) as evaluated from SINAN data by Burattini and Massad [30]. The risk function $R^L(a)$ (red line) was fitted using a piecewise defined function and is given by Equation (3.30).

strated in humans [87]. However, there still remains uncertainty about whether the disease severity is indeed determined by ADE. Some evidence for ADE is that 90-95% of severe dengue cases are due to secondary infections and the remaining severe dengue cases are usually associated with primary infections in infants that have some level of maternal antibodies [73, 84, 93]. Another hypothesis is that two heterologous infections confer PCI which is based on the fact that very few third and fourth infections are recorded [53, 54, 115]. Whether this is due to third and fourth infections being asymptomatic or whether individuals with two heterologous infections are protected against infection with a third serotype is not yet clear. If ADE plays an important role it is reasonable to assume that primary infections are asymptomatic and therefore risk-free. Similarly if there is PCI third and fourth infections are not associated with any risk. The four possible CRSs that will be considered are therefore

CRS (a): all infections are risky, i.e. neither ADE nor PCI are considered,

CRS (b): only primary infections are risk-free, i.e. ADE but no PCI is considered,

CRS (c): only post-secondary infections are risk-free, i.e. no ADE but PCI is considered, and

CRS (d): only secondary infections are risky, i.e. both ADE and PCI are considered.

The vaccination model that was described in Section 3.2.1 does not incorporate any cross-reactions between the different dengue serotypes as it is a single-serotype model. However, the lifetime expected risk can be used to consider such interdependencies. Particularly the risk functions associated with the infection probabilities given in Equations (3.24) and (3.25) for a specific infection and vaccination history or a specific infection history can be adapted to allow for the assumptions of ADE and PCI after two heterologous infections.

If there is no difference between previous natural infections or silent vaccine-induced infections cross-reactions between the different serotypes can easily be incorporated in the computation of the lifetime expected risk by setting certain risks to zero. For example, when ADE is considered to correspond to risk-free primary infections this can be done by putting $R_{i\bar{j}\bar{k}\bar{l}}(a) = 0$. Similarly PCI results in asymptomatic tertiary and quaternary infections, i.e. $R_{ij_+k_+\bar{l}}(a) = R_{ij_+\bar{k}l_+}(a) = R_{i\bar{j}k_+l_+}(a) = R_{ij_+k_+l_+}(a) = 0$. The remaining risk functions can simply be defined in terms of the risk of hospitalisation or lethality depending on which risk should be minimised through vaccination.

Setting the risks for primary or tertiary and quaternary infections or both to zero can still be done when vaccine-induced infections are considered to have a different effect than a natural infection. However, the definition of the remaining risk functions is slightly more complicated since an increased risk of hospitalisation during a subsequent dengue infection in seronegative vaccine recipients was observed. The previously obtained risk of hospitalisation is from the pre-vaccine era so that the risk functions need to be determined relative to this pre-vaccine risk. How this can be done will be discussed in detail in the next section.

## 3.5 Vaccine-Induced Risk

In addition to the possible CRSs there is also some uncertainty regarding the impact of Dengvaxia on the transmission dynamics and the disease severity. The initial safety and efficacy trials of Dengvaxia indicated the possibility of significantly reducing the burden of dengue [32, 66]. However, during the long-term follow-up of the vaccine trials an increased risk in seronegative recipients has been observed [132]. These new findings have forced the WHO to reconsider their recommendations for the use of the vaccine [133] and caused a considerable debate about whether and how Dengvaxia should be used [4–6, 38, 74, 75]. It is particularly questioned whether individuals who have not had a confirmed prior dengue infection should receive the vaccine at all. Ideally only seropositive individuals should receive the vaccine to prevent vaccine-induced hospitalisations, but with tests to determine the serostatus being expensive and unreliable this is not easily ensured. It is therefore necessary to consider the vaccine-induced risk to contribute to the lifetime expected risk.

This can be achieved by using relative risks to determine the relation between the risk functions associated with the probability of an infection for a specific infection and vaccination history and the pre-vaccine hospitalisation risk $R^H(a)$. Specifically the relative risks $\bar{h}^-(a)$, $\bar{h}^+(a)$, $h_*^-(a)$ and $h_*^+(a)$ for at risk unvaccinated seronegative individuals, at risk unvaccinated seropositive individuals, at risk successfully vaccinated initial seronegative individuals and at risk successfully vaccinated initial seropositive individuals respectively need to be defined. The definition of the first three of these relative risks depends on whether a primary infection is risky or not, i.e. if primary infections are risky they can be defined relative to unvaccinated seronegatives, whereas for risk-free primary infections they need to be defined relative to unvaccinated seropositives. So for example if primary infections are risky $\bar{h}^+(a)$ is the risk for an at risk unvaccinated seropos-

itive individual of age $a$ relative to an unvaccinated seronegative individual of age $a$. $h_*^+(a)$ will be defined as the risk of an at risk successfully vaccinated initially seropositive individual of age $a$ relative to the risk of an at risk unvaccinated seropositive individual of age $a$ both for risky and risk-free primary infections.

The hospitalisation cases in the vaccine and control groups during the Dengvaxia trials shown in Table 1.2 can be used to determine these relative risks for at risk individuals. However, the data presented in Table 1.2 cannot immediately be used with the previously described modelling framework. This has two reasons, namely the way in which the different CRSs and the vaccine-induced risk are modelled. In particular two things need to be considered to be able to determine the relative risks for each of the four CRSs from the data in Table 1.2. Firstly it needs to be taken account of the fact that not all hospitalisations in the vaccine group occurred in successfully vaccinated individuals. This is due to the fact that Dengvaxia is not 100% effective, i.e. not every individual that receives the vaccination is immunised. Secondly all hospitalisations need to be attributed to at risk individuals which depends on the considered CRS. In any case individuals who are seropositive to all four serotypes are no longer at risk since infection with any serotype confers lifelong immunity to that serotype. Additionally, if PCI after two heterologous infections is assumed, seropositive individuals with antibodies to at least two serotypes are no longer at risk and in the case of risk-free primary infections completely seronegatives are not yet at risk.

In order to obtain estimates of the data matching the model assumptions and thus determine the relative risks the probabilities in Equation (3.31) are defined for each of the four CRSs. Note that these risks are defined for the age-groups of the vaccine trials, i.e. $G_1$ is the age-class of individuals aged 2–8 years and $G_2$ is the age-class of individuals aged 9–16 years. For the pooled hospitalisation cases $G_0$ is defined as the age-class of all trial participants, i.e. individuals aged 2–16 years.

$$
\begin{aligned}
p_1(G_s) &= P(\text{an unvaccinated seropositive in age-class } G_s \text{ is} \\
&\qquad \text{at risk before the introduction of a vaccine}),\\
p_2(G_s) &= P(\text{an initial seronegative in age-class } G_s \text{ is successfully} \\
&\qquad \text{vaccinated and at risk immediately after vaccination}),\\
\widetilde{p}_2(G_s) &= P(\text{an initial seronegative in age-class } G_s \text{ is at risk} \\
&\qquad \text{immediately after vaccination given successful} \\
&\qquad \text{vaccinatation against at least one serotype}),\\
p_3(G_s) &= P(\text{an initial seropositive in age-class } G_s \text{ is successfully} \\
&\qquad \text{vaccinated and at risk immediately after vaccination}).
\end{aligned}
\tag{3.31}
$$

**Cross Reaction Scenario (a)**

The most basic case is when all infections are assumed risky. In this case only those individuals who have been infected by every serotype are no longer at risk. In particular seronegatives are at risk, so that for $a \in G_s$ the relative risks for individuals who are indeed at risk are defined by

$$\begin{aligned}
\bar{h}^-(a) &= \frac{P(\text{hospitalisation of an unvaccinated seronegative in age-class } G_s)}{P(\text{hospitalisation of an unvaccinated seronegative in age-class } G_s)} = 1,\\
\bar{h}^+(a) &= \frac{P(\text{hospitalisation of un unvaccinated seropositive in age-class } G_s)}{P(\text{hospitalisation of an unvaccinated seronegative in age-class } G_s)},\\
h_*^-(a) &= \frac{P(\text{hospitalisation of a successfully vaccinated initial seronegative in age-class } G_s)}{P(\text{hospitalisation of an unvaccinated seronegative in age-class } G_s)},\\
h_*^+(a) &= \frac{P(\text{hospitalisation of a successfully vaccinated initial seropositive in age-class } G_s)}{P(\text{hospitalisation of an unvaccinated seropositive in age-class } G_s)}.
\end{aligned} \tag{3.32}$$

Maternal antibodies decay quickly and since the trial cohort only included individuals aged at least 2 years it is reasonable to assume that the recorded number of seropositive individuals is due to prior natural infections and not due to passive immunity. $p_1(G_s)$ can therefore be obtained from the proportion of individuals in the age-class $G_s$ who are unaffected by serotype $i$ which will be denoted by

$$u_i^0(G_s) = \frac{\frac{N_H}{L}\int_{B_1}^{B_2} u_i^0(a)\pi_H(a)\,\mathrm{d}a}{\frac{N_H}{L}\int_{B_1}^{B_2} \pi_H(a)\,\mathrm{d}a} \tag{3.33}$$

where $B_1$ and $B_2$ are the limits of the age-class $G_s$ and

$$u_i^0(a) = e^{-\int_0^a \lambda_i^0(s)C_i(s)\,\mathrm{d}s}$$

is the pre-vaccine steady-state probability of being unaffected by serotype $i$ at age $a$. Any infection is risky so that seropositive individuals who are seropositive to at most three serotypes are at risk and therefore

$$p_1(G_s) = \frac{1 - u_1^0(G_s)u_2^0(G_s)u_3^0(G_s)u_4^0(G_s) - \prod_{i=1}^4 (1 - u_i^0(G_s))}{1 - u_1^0(G_s)u_2^0(G_s)u_3^0(G_s)u_4^0(G_s)}. \tag{3.34}$$

Clearly $p_2(G_s) = \widetilde{p}_2(G_s)\epsilon^-(G_s)$ where $\epsilon^-(G_s)$ is the vaccine efficacy for seronegatives as given in Table 1.1. A successfully vaccinated individual who was initially seronegative but remains at risk must have been vaccinated against at least one serotype but no more than three serotypes. Hence, from the serotype-specific

vaccine efficacies $\epsilon_i(G_s)$ as given in Table 1.1

$$\widetilde{p}_2(G_s) = \frac{1 - \epsilon_1(G_s)\epsilon_2(G_s)\epsilon_3(G_s)\epsilon_4(G_s) - \prod_{i=1}^{4}(1 - \epsilon_i(G_s))}{1 - \prod_{i=1}^{4}(1 - \epsilon_i(G_s))}. \tag{3.35}$$

Lastly an initial seropositive who was vaccinated successfully remains at risk only if they have antibodies to no more than three serotypes after vaccination, e.g. someone who was initially seropositive to one serotype remains at risk if they are successfully vaccinated against at most two serotypes. Therefore $p_3(G_s)$ depends on the probabilities $p_r^i(G_s)$ of an individual being seropositive to serotype $i$ and then successfully vaccinated against one or two other serotypes and $p_r^{ij}(G_s)$ of an individual being seropositive to serotypes $i$ and $j$ and then successfully vaccinated against exactly one other serotype. These probabilities are

$$p_r^i(G_s) = s^i(G_s)\epsilon^+(G_s)\frac{1 - \epsilon^j(G_s)\epsilon^k(G_s)\epsilon^l(G_s) - (1 - \epsilon^j(G_s))\left(1 - \epsilon^k(G_s)\right)\left(1 - \epsilon^l(G_s)\right)}{1 - (1 - \epsilon^j(G_s))\,(1 - \epsilon^k(G_s))\,(1 - \epsilon^l(G_s))}$$

$$p_r^{ij}(G_s) = s^{ij}(G_s)\epsilon^+(G_s)\frac{1 - \epsilon^k(G_s)\epsilon^l(G_s) - \left(1 - \epsilon^k(G_s)\right)\left(1 - \epsilon^l(G_s)\right)}{1 - (1 - \epsilon^k(G_s))\,(1 - \epsilon^l(G_s))}$$

with similar arguments where $\epsilon^+(G_s)$ denotes the vaccine efficacy for seropositives given by Table 1.1 and

$$s^i(G_s) = \frac{(1 - u_i^0(G_s))\,u_j^0(G_s)u_k^0(G_s)u_l^0(G_s)}{1 - u_i^0(G_s)u_j^0(G_s)u_k^0(G_s)u_l^0(G_s)}$$

$$s^{ij}(G_s) = \frac{(1 - u_i^0(G_s))\left(1 - u_j^0(G_s)\right)u_k^0(G_s)u_l^0(G_s)}{1 - u_i^0(G_s)u_j^0(G_s)u_k^0(G_s)u_l^0(G_s)}$$

denote the age-class distributions of seropositivity to serotype $i$ only given that an individual is seropositive, and serotypes $i$ and $j$ only given that an individual is seropositive, respectively. Hence,

$$p_3(G_s) = \sum_{i=1}^{4} p_r^i(G_s) + \sum_{\substack{i,j=1 \\ i \neq j}}^{4} p_r^{ij}(G_s). \tag{3.36}$$

Table 1.2 shows that there were 236 and 481 seropositive individuals in the control group and in the vaccine group aged 2–8 respectively. $236p_1(G_1)$ and $481p_3(G_1)$ of them were in fact at risk. Of the 330 initial seronegatives aged 2–8 in the vaccine group $330p_2(G_1)$ were at risk and $330\,(1 - \epsilon^-(G_1))$ were not successfully vaccinated but caused an expected $330\,(1 - \epsilon^-(G_1))\,\frac{5}{173}$ of the 17 hospitalisations recorded. For the age-group 9–16 years it can be argued similarly.

The relative risks are thus

$$
\begin{aligned}
\bar{h}^{-}(a) &= 1, \\
\bar{h}^{+}(a) &= \begin{cases} \frac{11}{236p_1(G_1)} \Big/ \frac{5}{173}, & 0 \leq a < 9, \\ \frac{15}{752p_1(G_2)} \Big/ \frac{4}{204}, & 9 \leq a < \infty, \end{cases} \\
h_*^{-}(a) &= \begin{cases} \frac{17-330\left(1-\epsilon^{-}(G_1)\right)\frac{5}{173}}{330p_2(G_1)} \Big/ \frac{5}{173}, & 0 \leq a < 9, \\ \frac{7-382\left(1-\epsilon^{-}(G_2)\right)\frac{4}{204}}{382p_2(G_2)} \Big/ \frac{4}{204}, & 9 \leq a < \infty, \end{cases} \\
h_*^{+}(a) &= \begin{cases} \frac{9}{481p_3(G_1)} \Big/ \frac{11}{236p_1(G_1)}, & 0 \leq a < 9, \\ \frac{7}{1{,}546p_3(G_2)} \Big/ \frac{15}{752p_1(G_2)}, & 9 \leq a < \infty \end{cases}
\end{aligned}
\tag{3.37}
$$

where it is assumed that individuals below 2 years of age experience the same relative risk as those in the age-group 2–8 years and individuals above 16 years of age experience the same as those in the age-group 9–16 years.

However the age-dependence of the vaccine-induced risk in seronegative recipients as well as in the vaccine efficacy is still being challenged [4, 5, 38, 75]. It might therefore be better to pool the recorded hospitalisation cases as shown in Table 1.2 and instead consider age-group independent relative risks based on the age-class of individuals aged 2–16 years that are applied to individuals of any age.
They are obtained as

$$
\begin{aligned}
\bar{h}^{-}(a) &= 1, \\
\bar{h}^{+}(a) &= \frac{26}{988p_1(G_0)} \Big/ \frac{9}{377}, \\
h_*^{-}(a) &= \frac{24-712\left(1-\epsilon^{-}(G_0)\right)\frac{9}{377}}{712p_2(G_0)} \Big/ \frac{9}{377}, \\
h_*^{+}(a) &= \frac{16}{2{,}027p_3(G_0)} \Big/ \frac{26}{988p_1(G_0)}.
\end{aligned}
\tag{3.38}
$$

Having determined the relative risks for seronegative and seropositive unvaccinated individuals the pre-vaccine hospitalisation risk can be expressed in terms of the pre-vaccine hospitalisation risks for seronegatives $R_{-}^{H}(a)$ and seropositives $R_{+}^{H}(a)$. Any seronegative and seropositives with antibodies to no more than three serotypes are at risk, so that

$$
\begin{aligned}
R^H(a) &= u_1^0(a)u_2^0(a)u_3^0(a)u_4^0(a)R_-^H(a) + \Big[1 - u_1^0(a)u_2^0(a)u_3^0(a)u_4^0(a) \\
&\quad - \Big(1 - u_1^0(a)\Big)\Big(1 - u_2^0(a)\Big)\Big(1 - u_3^0(a)\Big)\Big(1 - u_4^0(a)\Big)\Big] R_+^H(a), \\
&= \Big\{u_1^0(a)u_2^0(a)\, u_3^0(a)u_4^0(a) + \Big[1 - u_1^0(a)u_2^0(a)u_3^0(a)u_4^0(a) \\
&\quad - \Big(1 - u_1^0(a)\Big)\Big(1 - u_2^0(a)\Big)\Big(1 - u_3^0(a)\Big)\Big(1 - u_4^0(a)\Big)\Big] \bar{h}^+(a)\Big\} R_-^H(a).
\end{aligned} \tag{3.39}
$$

The risk functions associated with the infection probabilities given in Equation (3.24) can then be determined as

$$
\begin{aligned}
&R_{i\bar{j}\bar{k}\bar{l}}(a) = \bar{h}^-(a)R_-^H(a) = R_-^H(a), \\
&R_{ijkl}(a) = R_{ijk\bar{l}}(a) = R_{ij\bar{k}\bar{l}}(a) = \bar{h}^+(a)R_-^H(a), \\
&R_{ij_*k_*l_*}(a) = R_{ij_*k_*\bar{l}}(a) = R_{ij_*\bar{k}\bar{l}}(a) = h_*^-(a)R_-^H(a), \\
&R_{ijkl_*}(a) = R_{ijk_*l_*}(a) = R_{ijk_*\bar{l}}(a) = h_*^+(a)R_+^H(a) = h_*^+(a)\bar{h}^+(a)R_-^H(a),
\end{aligned} \tag{3.40}
$$

where it is assumed that once an individual has both vaccine-induced antibodies and antibodies due to a natural infection the risk does not depend on whether the vaccination or infection took place first.

We shall look at CRS (b) later since a redefinition of the relative risks $\bar{h}^-(a)$, $\bar{h}^+(a)$ and $h_*^-(a)$ in terms of at risk unvaccinated seronegatives is necessary in this scenario. Now we will continue by looking at CRS (c) where the definition of all relative risks remains the same and only the probabilities $p_1(G_s)$, $p_2(G_s)$ and $p_3(G_s)$ need to be adapted to take account of the fact that due to the PCI individuals who are seropositive to two or more serotypes are no longer at risk.

### Cross Reaction Scenario (c)

In the case of risky primary infections but risk-free post-secondary infections, i.e. PCI, the relative risks are defined as before. However, since now only seropositive individuals who are seropositive to exactly one serotype remain at risk

$$
p_1(G_s) = \frac{\sum_{i=1}^{4}\Big[\big(1 - u_i^0(G_s)\big)\, u_j^0(G_s)u_k^0(G_s)u_l^0(G_s)\Big]}{1 - u_1^0(G_s)u_2^0(G_s)u_3^0(G_s)u_4^0(G_s)}, \tag{3.41}
$$

$$
\text{and} \quad p_2(G_s) = \frac{\sum_{i=1}^{4}\left[\epsilon_i(G_s)\left(1 - \epsilon_j(G_s)\right)\left(1 - \epsilon_k(G_s)\right)\left(1 - \epsilon_l(G_s)\right)\right]}{1 - \left(1 - \epsilon_1(G_s)\right)\left(1 - \epsilon_2(G_s)\right)\left(1 - \epsilon_3(G_s)\right)\left(1 - \epsilon_4(G_s)\right)}\epsilon^-(G_s) \tag{3.42}
$$

with similar arguments as before. Further $p_3(a)$ is clearly zero as any seropositive who is successfully vaccinated will be seropositive to at least two serotypes. By definition $h_*^+(a) = 0$. Assuming again that individuals below the lower age limit of the age-class $G_1$ have the same risk as individuals in this age-range and similarly for individuals above the upper age limit of the age-class $G_2$ the relative risks are

$$\begin{aligned}
\bar{h}^-(a) &= 1, \\
\bar{h}^+(a) &= \begin{cases} \frac{11}{236p_1(G_1)} \Big/ \frac{5}{173}, & 0 \le a < 9, \\ \frac{15}{752p_1(G_2)} \Big/ \frac{4}{204}, & 9 \le a < \infty, \end{cases} \\
h_*^-(a) &= \begin{cases} \frac{17-330\left(1-\epsilon^-(G_1)\right)\frac{5}{173}}{330p_2(G_1)} \Big/ \frac{5}{173}, & 0 \le a < 9, \\ \frac{7-382\left(1-\epsilon^-(G_2)\right)\frac{4}{204}}{382p_2(G_2)} \Big/ \frac{4}{204}, & 9 \le a < \infty, \end{cases} \\
h_*^+(a) &= 0,
\end{aligned} \tag{3.43}$$

and

$$\begin{aligned}
\bar{h}^-(a) &= 1, \\
\bar{h}^+(a) &= \frac{26}{988p_1(G_0)} \Big/ \frac{9}{377}, \\
h_*^-(a) &= \frac{24-712\left(1-\epsilon^-(G_0)\right)\frac{9}{377}}{712p_2(G_0)} \Big/ \frac{9}{377}, \\
h_*^+(a) &= 0
\end{aligned} \tag{3.44}$$

if the data is pooled.

Similarly to before we have that

$$\begin{aligned}
R^H(a) &= u_1^0(a)u_2^0(a)u_3^0(a)u_4^0(a)R_-^H(a) + \sum_{i=1}^{4}\left[(1-u_i^0(a))u_j^0(a)u_k^0(a)u_l^0(a)\right]R_+^H(a), \\
&= \left\{u_1^0(a)u_2^0(a)u_3^0(a)u_4^0(a) + \sum_{i=1}^{4}\left[(1-u_i^0(a))u_j^0(a)u_k^0(a)u_l^0(a)\right]\bar{h}^+(a)\right\}R_-^H(a),
\end{aligned} \tag{3.45}$$

and the risk functions are given by

$$\begin{aligned}
&R_{i\bar{j}\bar{k}\bar{l}}(a) = \bar{h}^-(a)R_-^H(a) = R_-^H(a), \\
&R_{ij\bar{k}\bar{l}}(a) = \bar{h}^+(a)R_-^H(a), \\
&R_{ij_*\bar{k}\bar{l}}(a) = h_*^-(a)R_-^H(a), \\
&R_{ijkl}(a) = R_{ijk\bar{l}}(a) = R_{ij_*k_*l_*}(a) = R_{ij_*k_*\bar{l}}(a) = R_{ijkl_*}(a) = R_{ijk_*l_*}(a) = R_{ijk_*\bar{l}}(a) = 0,
\end{aligned} \tag{3.46}$$

where tertiary and quaternary infections are risk-free due to PCI. In the risk functions the order of prior infection and vaccination does not matter, i.e. for $R_{ij_*k\bar{l}}(a)$ it is irrelevant whether the infection with serotype $k$ occurred before the successful vaccination against serotype $j$ or vice versa.

We will now move onto CRS (b) and CRS (d) where risk-free primary infections are assumed and hence all relative risks need to be defined in terms of the risk of unvaccinated seropositives.

### Cross Reaction Scenario (b)

The case in which primary infections are assumed risk-free requires a re-definition of $\bar{h}^-(a)$, $\bar{h}^+(a)$ and $h_*^-(a)$ relative to the risk of unvaccinated seropositive individuals since unvaccinated seronegative individuals are not yet at risk. For $a \in G_s$ the relative risks are therefore defined by

$$\begin{aligned}
\bar{h}^-(a) &= \frac{P(\text{hospitalisation of an unvaccinated seronegative in age-class } G_s)}{P(\text{hospitalisation of an unvaccinated seropositive in age-class } G_s)} = 0,\\
\bar{h}^+(a) &= \frac{P(\text{hospitalisation of an unvaccinated seropositive in age-class } G_s)}{P(\text{hospitalisation of an unvaccinated seropositive in age-class } G_s)} = 1,\\
h_*^-(a) &= \frac{P(\text{hospitalisation of a successfully vaccinated initial seronegative in age-class } G_s)}{P(\text{hospitalisation of an unvaccinated seropositive in age-class } G_s)},\\
h_*^+(a) &= \frac{P(\text{hospitalisation of a successfully vaccinated initial seropositive in age-class } G_s)}{P(\text{hospitalisation of an unvaccinated seropositive in age-class } G_s)}
\end{aligned} \tag{3.47}$$

and can be determined in a very similar manner to the case of all infections being risky. In fact, the only relative risk that needs to be calculated in this case is $h_*^-(a)$ since the definition of $h_*^+(a)$ has not changed and $\bar{h}^-(a)$ and $\bar{h}^+(a)$ are already determined by their definitions. Take $p_1(G_s)$, $p_2(G_s) = \widetilde{p}_2(G_s)\epsilon^-(G_s)$ and $p_3(G_s)$ as given by Equations (3.34) to (3.36), then the relative risks when the age-groups of the vaccine trials are taken account of are computed as

$$\begin{aligned}
\bar{h}^-(a) &= 0,\\
\bar{h}^+(a) &= 1,\\
h_*^-(a) &= \begin{cases} \frac{17-330\left(1-\epsilon^-(G_1)\right)\frac{5}{173}}{330p_2(G_1)} \Big/ \frac{11}{236p_1(G_1)}, & 0 \le a < 9,\\ \frac{7-382\left(1-\epsilon^-(G_2)\right)\frac{4}{204}}{382p_2(G_2)} \Big/ \frac{15}{752p_1(G_2)}, & 9 \le a < \infty, \end{cases}\\
h_*^+(a) &= \begin{cases} \frac{9}{481p_3(G_1)} \Big/ \frac{11}{236p_1(G_1)}, & 0 \le a < 9,\\ \frac{7}{1{,}546p_3(G_2)} \Big/ \frac{15}{752p_1(G_2)}, & 9 \le a < \infty. \end{cases}
\end{aligned} \tag{3.48}$$

Otherwise they are

$$\begin{aligned}
\bar{h}^-(a) &= 0,\\
\bar{h}^+(a) &= 1,\\
h_*^-(a) &= \frac{24-712\left(1-\epsilon^-(G_0)\right)\frac{9}{377}}{712p_2(G_0)} \Big/ \frac{26}{988p_1(G_0)},\\
h_*^+(a) &= \frac{16}{2{,}027p_3(G_0)} \Big/ \frac{26}{988p_1(G_0)}.
\end{aligned} \tag{3.49}$$

$R^H(a)$ can be expressed in terms of $R_+^H(a)$ since risk-free primary infections imply $R_-^H(a) = 0$. There is no PCI after two heterologous infections so that third and fourth infections are symptomatic and only individuals who are seropositive to all four serotypes are no longer at risk. Therefore

$$\begin{aligned}
R^H(a) = \Big[1 &- u_1^0(a)u_2^0(a)u_3^0(a)u_4^0(a)\\
&- \left(1-u_1^0(a)\right)\left(1-u_2^0(a)\right)\left(1-u_3^0(a)\right)\left(1-u_4^0(a)\right)\Big] R_+^H(a).
\end{aligned} \tag{3.50}$$

The risk functions associated with a specific infection and vaccination history are

$$\begin{aligned}
&R_{i\bar{j}\bar{k}\bar{l}}(a) = 0,\\
&R_{ijkl}(a) = R_{ijk\bar{l}}(a) = R_{ij\bar{k}\bar{l}}(a) = \bar{h}^+(a)R_+^H(a) = R_+^H(a),\\
&R_{ij_*k_*l_*}(a) = R_{ij_*k_*\bar{l}}(a) = R_{ij_*\bar{k}\bar{l}}(a) = h_*^-(a)R_+^H(a),\\
&R_{ijkl_*}(a) = R_{ijk_*l_*}(a) = R_{ijk_*\bar{l}}(a) = h_*^+(a)R_+^H(a).
\end{aligned} \tag{3.51}$$

Again the order of prior infection and vaccination does not matter.

### Cross Reaction Scenario (d)

Lastly consider both primary and post-secondary infections to be risk-free. The definitions of the relative risks are as in CRS (b). Only individuals who are seropositive to exactly one serotype are at risk. $p_1(G_s)$ and $p_2(G_s) = \widetilde{p}_2(G_s)\epsilon^-(G_s)$ are therefore given by Equations (3.41) and (3.42). The age-group dependent relative risks are then

$$\begin{aligned}
\bar{h}^-(a) &= 0,\\
\bar{h}^+(a) &= 1,\\
h_*^-(a) &= \begin{cases} \frac{17-330\left(1-\epsilon^-(G_1)\right)\frac{5}{173}}{330p_2(G_1)} \Big/ \frac{11}{236p_1(G_1)}, & 0 \le a < 9,\\ \frac{7-382\left(1-\epsilon^-(G_2)\right)\frac{4}{204}}{382p_2(G_2)} \Big/ \frac{15}{752p_1(G_2)}, & 9 \le a < \infty, \end{cases}\\
h_*^+(a) &= 0.
\end{aligned} \tag{3.52}$$

If the data is instead pooled, the relative risks are

$$\begin{aligned}
\bar{h}^-(a) &= 0,\\
\bar{h}^+(a) &= 1,\\
h_*^-(a) &= \frac{24-712\left(1-\epsilon^-(G_0)\right)\frac{9}{377}}{712p_2(G_0)} \Big/ \frac{26}{988p_1(G_0)},\\
h_*^+(a) &= 0,
\end{aligned} \tag{3.53}$$

and since only secondary infections are risky

$$R^H(a) = \sum_{i=1}^{4} \left[\left(1-u_i^0(a)\right) u_j^0(a)u_k^0(a)u_l^0(a))\right] R_+^H(a). \tag{3.54}$$

Therefore

$$\begin{aligned}
&R_{ij\bar{k}\bar{l}}(a) = \bar{h}^+(a)R^+(a) = R_+^H(a),\\
&R_{ij_*\bar{k}\bar{l}}(a) = h_*^-(a)R_+^H(a),\\
&R_{ijkl}(a) = R_{ijk\bar{l}}(a) = R_{i\bar{j}\bar{k}\bar{l}}(a) = 0,\\
&R_{ij_*k_*l_*}(a) = R_{ij_*k_*\bar{l}}(a) = R_{ijkl_*}(a) = R_{ijk_*l_*}(a) = R_{ijk_*\bar{l}}(a) = 0,
\end{aligned} \tag{3.55}$$

where the order of the prior infections and successful vaccination is again irrelevant.

## 3.6 Summary

In this chapter a single-serotype transmission model was introduced in which the age-densities of unaffected, infected and recovered humans and the total numbers of susceptible, latent and infectious mosquitoes were modelled. The force of infection and proportions of unaffected, infected and recovered humans were derived at the endemic steady-state. The basic reproduction number for the model was inferred from its definition as the number of secondary infections one infected individual generates in an otherwise completely susceptible population at the steady-state. Additionally an alternative expression using easily attainable model parameters was obtained by linearisation.

From the steady-state dynamics the risk of an infection with a given dengue serotype at age $a$ was defined based on the infection and vaccination history of an individual, i.e. when vaccine-induced antibodies and naturally acquired antibodies behave differently, or on the infection history of an individual only where no

difference is assumed between antibodies caused by successful vaccination or by a natural infection. The lifetime expected risk was subsequently defined as the risk caused by all serotypes during the entire lifetime of an individual. For both of these definitions it is necessary to assign some undesirability to an infection with dengue. There are several possible measures of undesirability. However, getting infected by dengue does often not have any consequences for an individual due to infections being asymptomatic. It is therefore better to base the risk on some adverse effect of an infection rather than on becoming infected per se. In this chapter the risk of hospitalisation or lethality due to a dengue infection was therefore derived from data that pre-dates the introduction of Dengvaxia in Brazil.

Considering the different theories regarding possible serotype interactions such as ADE and PCI after two heterologous infections four CRSs were identified. In particular ADE was assumed to imply that primary infections are risk-free and similarly PCI that post-secondary infections are risk-free. The risk functions were adapted for each of these scenarios to take account of this. In the case of there not being a difference between vaccine-induced antibodies and naturally acquired antibodies this can be done by simply setting the corresponding risk functions to zero. However, more work was required in the case of vaccine-induced antibodies being considered separately. In particular the recorded number of hospitalisations during the long-term follow-up of the Dengvaxia trials was used to determine relative risks for seronegative and seropositive individuals who have or have not been successfully vaccinated.

This modelling framework can now be used to find the optimal vaccination age against dengue for any number and combination of serotypes. Note that the lifetime expected risk was defined in such a way that it is possible to consider several serotypes even though the model only reflects the transmission dynamics of a single serotype. In a first step it is necessary to determine the lifetime expected risk for any vaccination age. The optimal vaccination age is then identified as the age resulting in the lowest lifetime expected risk.

In the next three chapters the modelling framework will be used to determine the optimal vaccination age for different assumptions. In Chapter 4 the model will be used in a slightly simplified version with a constant human death rate and a constant biting rate. This made the initial analysis easier and can still give some indication of the optimal vaccination ages. The risk of hospitalisation and lethality when only the infection history of an individual is considered will be minimised in this chapter for both a constant and an age-dependent vaccine

efficacy and for all CRSs.

In Chapter 5 the model will be used with a more realistic step-death function for the human population and the biting rate will be derived as a function depending on the age of the human from mosquito biting data. Again the risk of hospitalisation and lethality when only the infection history of an individual is considered will be minimised. However, due to recent data indicating an increased hospitalisation risk in some vaccine recipients which resulted in a revision of the official vaccination guideline the risk of hospitalisation when the infection and vaccination history of an individual influences the risk will additionally be considered. It is still unclear whether the negative effect is partly caused by the age or only due to serostatus. The vaccine-induced risk will therefore be considered to be constant or age-dependent based on the age-groups determined during the vaccine trials. If the increased risk is not assumed to depend on the age of the recipient the age-groups of the Dengvaxia trial are entirely disregarded, i.e. both the vaccine-induced risk and the vaccine efficacy are assumed constant. Again all CRSs will be considered.

In Chapter 6 a model with a human step-death function and an age-dependent biting rate will be used. However, instead of determining the biting rate from mosquito biting data and using this biting rate to determine the force of infection, serological data pre-dating the introduction of Dengvaxia in Brazil will be used to find the age-dependent force of infection at the pre-vaccine steady-state. The same assumptions regarding the risk of an infection with dengue will be made as in Chapter 5 and both constant and age-dependent efficacy and vaccine-induced risk will be considered for all CRSs.

Finally, in Chapter 7, the findings from Chapters 4 to 6 will be summarised and compared. In particular the effect of the different model assumptions, risk functions, CRSs and vaccine related factors such as the age-dependence of the efficacy and the vaccine-induced risk on the optimal vaccination age will be discussed. It will also be highlighted in which direction the work of this thesis can be continued to determine the optimal vaccination age for dengue in Brazil most accurately.

Chapter 4

# Optimal Vaccination Age with a Constant Biting Rate

## 4.1 Introduction

The modelling framework derived in the previous chapter can be used to obtain the optimal vaccination age in a specific endemic area for any defined undesirability of an infection with dengue and for a given CRS. However, the model presented in Section 3.2 was in fact developed from a simplified version where the human death rate and the biting rate were assumed constant. Both of these assumptions are only approximations of the facts but made the initial steady-state analysis easier. A constant death rate is not a particularly realistic approximation for a country like Brazil but is a commonly used simplification in epidemiological modelling [11]. Similarly humans are actually bitten by mosquitoes with varying frequencies depending on their age. This is due to different behaviour, as children may, for example, spend a significant amount of time outside but are not preoccupied with having to protect themselves from mosquito bites. However, as an initial approximation a constant biting rate can still be used to gain some insight into the effects of different assumptions on the optimal vaccination age.

In this chapter the previously derived model will therefore be used with a constant biting rate and a constant human death rate to obtain the optimal vaccination age for dengue. While the majority of the theoretical work was already carried out in the previous chapter the most important theoretical results for these model assumptions will briefly be summarised in the next section. Subsequently the serotype-specific effective reproduction numbers will be inferred from case report data provided by SINAN. These can then be used to calculate

the serotype-specific forces of infection for a specific vaccination strategy and hence the lifetime expected risk. By minimising the lifetime expected risk the optimal vaccination age can be obtained. The results both for the risk of hospitalisation and lethality will be presented where every CRS will be considered both for age-independent and age-dependent vaccine efficacies as given in Table 1.1. Dengvaxia is only licensed for the use in individuals aged 9 to 45 years in Brazil so that in addition to the optimal vaccination age, the age that minimises the lifetime expected risk under this constraint will be determined. The findings will ultimately be summarised and compared for the different assumptions and the consequences of the age-restriction will be discussed. Vaccine-induced risk is not considered in this chapter since the simulations were carried out before the consensus was reached that Dengvaxia increases the risk in seronegative recipients. Our vaccination assumptions reflect the official vaccination policy as it was at the time when these simulations were carried out. They were later changed due to an increased risk in seronegative recipients as discussed in Section 1.4.3. Throughout this chapter the lifetime expected risk is therefore computed from the expected risk from an infection with serotype $i$ at age $a$ given by Equation (3.27).

## 4.2 Model Assumptions

In the previous chapter the modelling framework required to determine the optimal vaccination age for dengue was derived. The model given in Equations (3.3) to (3.5) describes the transmission dynamics for a single serotype and the effect of vaccination on these dynamics. However, the lifetime expected risk $E$, cf. Equation (3.28), was defined for all four dengue serotypes and makes it possible to consider different CRSs both for the risk of hospitalisation and lethality. This framework can also be used for a slightly simplified model where both the human death rate and the rate at which mosquitoes bite humans are assumed to be constant.

The steady-state analysis for the general model was already carried out in Section 3.2.2 to find the steady-state force of infection given by Equation (3.15) and the steady-state age-densitities of unaffected humans $u(a)$, infected humans $i(a)$ and recovered humans $r(a)$ respectively. These age-densities are necessary to compute the lifetime expected risk. Additionally the basic reproduction number as well as an approximate expression for it was derived in Section 3.2.3. The model was introduced with an age-dependent death rate $\mu_H(a)$ for humans and an age-dependent biting rate $q(a)$. However, assuming constant rates $\mu_H$ and $q$

as an approximation makes the analysis easier. $\mu_H = 0.01355$ per year was taken from the literature [153]. In this case the survival probability is $\pi_H(a) = e^{-\mu_H a}$ resulting in the life expectancy $L = \frac{1}{\mu_H} = 73.8$ years and therefore the age-density function at the steady-state for the total human population is given by

$$N(a) = \mu_H N_H e^{-\mu_H a}. \tag{4.1}$$

The force of infection for humans is age-independent since $q$ is a constant. At the steady-state it is given by

$$\begin{aligned} \lambda &= \lim_{t\to\infty} qb\frac{I_M(t)}{N_H}, \\ &= \frac{q^2bcme^{-\mu_M\tau}}{\mu_M L}\frac{\int_0^\infty i(a)e^{-\mu_H a}\,\mathrm{d}a}{1+\frac{qc}{\mu_M L}\int_0^\infty i(a)e^{-\mu_H a}\,\mathrm{d}a}, \end{aligned} \tag{4.2}$$

but can be expressed in terms of the basic reproduction number $R_0$. In particular

$$\lambda = R_0\frac{\mu_H+\gamma_H}{L}\frac{\int_0^\infty i(a)e^{-\mu_H a}\,\mathrm{d}a}{1+\frac{qc}{\mu_M L}\int_0^\infty i(a)e^{-\mu_H a}\,\mathrm{d}a}. \tag{4.3}$$

where

$$\begin{aligned} R_0 &\approx \frac{q^2bcme^{-\mu_M\tau}}{\mu_M\left(\mu_H+\gamma_H\right)}, \\ &\approx e^{\alpha\tau}\frac{\left(\alpha+\mu_M\right)\left(\alpha+\mu_H+\gamma_H\right)}{\mu_M\left(\mu_H+\gamma_H\right)}, \end{aligned} \tag{4.4}$$

can be obtained from Equations (3.19) and (3.22) by integration with a constant biting rate and a constant death rate if it is assumed that $C(a) \equiv 1$ since maternal antibodies decline quickly. The initial exponential growth rate of an epidemic, $\alpha$, is used to approximate the basic reproduction number as outlined in Section 3.2.3 and this parameter can be inferred from case report data [102, 103]. This approach can be used for each serotype separately to obtain serotype-specific effective reproduction numbers as will be done in the following section. Note that since dengue has been endemic in Brazil for decades the derived numbers are effective rather than basic reproduction numbers. However, as an approximation the same approach can be used.

## 4.3 Effective Reproduction Numbers

The Brazilian National Notifiable Diseases Information System (SINAN) was first set up in 1993 to enable the collection of data on various notifiable diseases such as dengue [25]. A significant amount of information is collected for each case, such as the patient's age, educational level and medical history [26]. The weekly number of dengue cases reported through SINAN between 2000 and 2014 were provided for the five regions North, North-East, South, South-East and Centre-West. The case report data was separated by serotype whenever the infecting serotype was determined. These serotype-specific weekly case numbers can be used to find the initial phase of an outbreak. In particular the exponential growth rate $\alpha_i$ for the serotype $i = 1, 2, 3, 4$ can be determined and thus the effective reproduction number for serotype $i$ can be computed from Equation (4.4).

In the years from 2000 to 2014 DENv1, DENv2 and DENv3 each caused four major epidemics in Brazil. On the other hand DENv4 was responsible for just two epidemics - one in 2012 and the other in 2013. There were no earlier outbreaks with this serotype documented in the data since it only re-emerged in Brazil in 2010 after an absence of 28 years [114]. From the nationwide weekly incidence data the first twelve weeks of each of these outbreaks were determined for Brazil as a whole to obtain the initial growth rate $\alpha_i$ for the corresponding serotype. Additionally the initial phase of the outbreaks was determined for each of the five regions separately to obtain upper and lower bounds for $\alpha_i$. In each of the regions there are different climatic conditions so that the start of the epidemics varied slightly between the regions and it is difficult to determine the start exactly. The effective reproduction numbers presented in Table 4.1 were obtained by using

Table 4.1: Estimates of the serotype-specific effective reproduction numbers obtained from the initial exponential growth rate of epidemics when the transmission dynamics are modelled with a constant biting rate and human death rate. The data comprises all epidemics in Brazil between 2000 and 2014 for each serotype. The upper and lower bounds are taken from the highest and lowest exponential growth rates of the outbreaks in the regions North, North-East, South, South-East and Centre-West during the same period.

| Serotype | $R_e$ | lower bound | upper bound |
|---|---|---|---|
| DENv1 | 4.7042 | 1.2230 | 6.1772 |
| DENv2 | 2.9941 | 1.3745 | 8.5126 |
| DENv3 | 4.2972 | 1.4341 | 13.4116 |
| DENv4 | 4.1861 | 1.8291 | 4.8708 |

the mean value of $\alpha$ for nationwide epidemics caused by each specific serotype in Equation (4.4) where the remaining parameter values were taken from the literature as given in Table 3.1. The upper and lower bounds were calculated by considering the highest and lowest values of $\alpha$ for the different regions. This approach has been used before for several diseases including dengue [50, 102, 103]. The values obtained for the effective reproduction numbers seem to be in agreement with other estimates even though the exact values of $\alpha$ highly depend on which weeks are taken to correspond to the start of an outbreak.

## 4.4 Optimal Vaccination Age

The serotype-specific effective reproduction numbers that were determined in the previous section can be used to compute $q$ from Equation (4.4) and thus the steady-state force of infection as the solution of Equation (4.3) (note that $i(a)$ depends on $\lambda$). This can be done for each serotype, any vaccination age and different assumptions relating to the age-dependence of the vaccine efficacy. Once the forces of infection for all four serotypes are known the lifetime expected risk and the optimal vaccination age can be obtained for the different CRSs both for the risk of hospitalisation and lethality. The vaccination schedule that leads to the lowest lifetime expected risk is considered optimal. Dengvaxia is licensed to be administered in three doses given at an interval of 6 months. The simulated vaccination strategies all adhere to this pattern. The vaccination age $A_1$ at which the first of the three doses is given and that results in the minimal lifetime expected risk is then referred to as the optimal vaccination age, i.e. the age at which vaccination should ideally be initiated.

The optimal vaccination age will be determined firstly to minimise the risk of hospitalisation and subsequently to minimise the risk of lethality. In both cases all CRSs will be considered and the expected risk from an infection will be assumed to depend on the infection history of the individual only rather than on the infection and vaccination history (cf. Equation (3.27)). All results will be presented for age-independent and age-dependent serotype-specific vaccine efficacies. Results using an age-independent vaccine efficacy will further be discussed in detail for endemic areas with any number of serotypes, while for age-dependent vaccine efficacy the differences are briefly highlighted by considering an endemic area with a single serotype only. Finally the effect of restricting the vaccination age to be between 9 and 45 years according to Dengavaxia's licence will be examined.

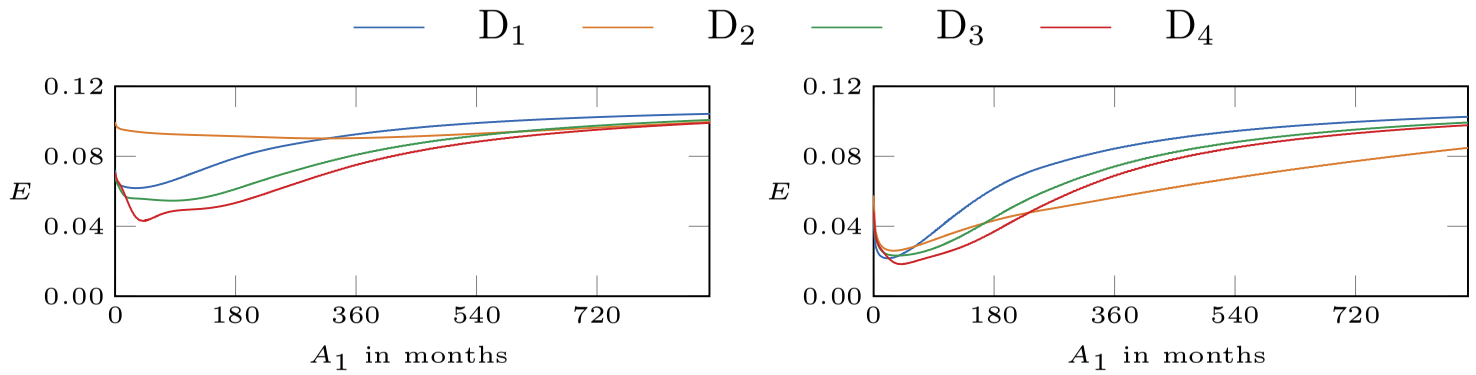
### 4.4.1 Minimising the Risk of Hospitalisation

Reducing the number of hospitalisations caused by dengue infections can significantly reduce the economic burden of dengue. However, in order to maximise the impact on the burden the optimal vaccination strategy needs to be chosen. The ideal strategy depends on several factors, first and foremost on the vaccine efficacy. The vaccine efficacy was found to be age-dependent in several phase three trials [32, 66] with a higher efficacy in children above the age of 9 years than in younger children (cf. Table 1.1). However, it is argued that the vaccine efficacy actually increases when an individual is seropositive which is more likely at older ages, i.e. the serostatus rather than age per se determines the vaccine efficacy. The optimal vaccination age will therefore be determined first for a constant efficacy and then for an age-dependent one as given in Table 1.1. Subsequently the effect of the licence restriction on the vaccination age will be discussed in both cases.

#### Constant Vaccine Efficacy

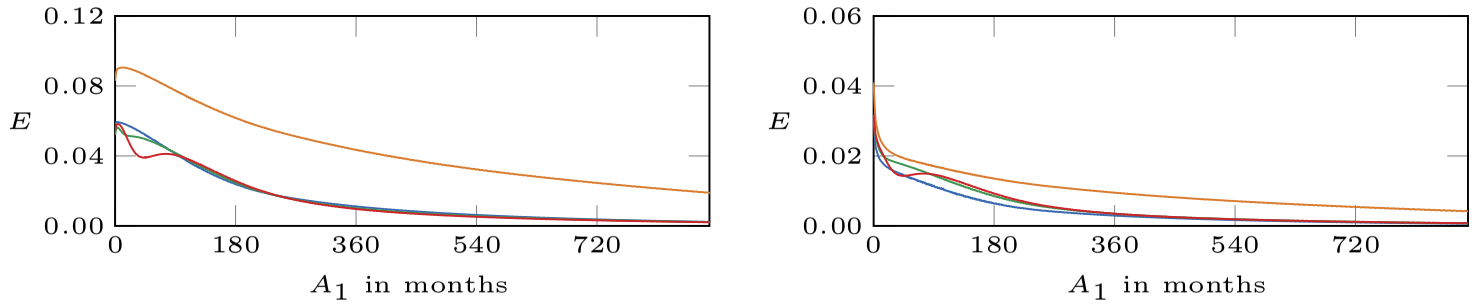
In most endemic countries several of the dengue virus serotypes DENv1–4 coexist. However, in order to understand the effect of the different effective reproduction numbers, efficacies, and rates of decay of maternal antibodies for the four serotypes to begin with an endemic region with a single serotype in existence will be considered. Note that while only a single serotype exists infections are not necessarily primary infections due to the tetravalence of the vaccine. Vaccination corresponds to a silent infection with the serotypes it successfully immunised against, so that a natural infection after a successful vaccination can be a secondary, tertiary or quaternary infection. The results for such an endemic region with a single circulating serotype are presented in Figure 4.1 where the subfigures (a)–(d) correspond to the CRS (a)–(d) respectively. Recall that CRS (a) and CRS (c) consider risky primary infections, while CRS (b) and CRS (d) consider risk-free primary infections based on the theory of ADE. CRS (c) and CRS (d) are based on few third and fourth infections being recorded, i.e. tertiary and quaternary infections are assumed risk-free in these scenarios. The graph shows the lifetime expected risk $E$ as a function of the vaccination age $A_1$ at which the first of three doses is given. The optimal vaccination age is that at which the lifetime expected risk reaches its minimum.

CRS (a) is shown in Figure 4.1a. In order to understand the effect of the different efficacies DENv3 and DENv4 can be compared. These two serotypes have very similar effective reproduction numbers of approximately 4.3 and 4.2 respectively.




(a) The optimal vaccination ages for DENv1, DENv2, DENv3 and DENv4 are 31, 311, 85 and 42 months respectively.

(c) The optimal vaccination ages for DENv1, DENv2, DENv3 and DENv4 are 22, 31, 36 and 42 months respectively.




(b) Vaccination is not recommended for any serotype.

(d) Vaccination is not recommended for any serotype.

Figure 4.1: The lifetime expected risk $E$ of hospitalisation in an endemic area where a single serotype exists as a function of age $A_1$ at which the first vaccine dose is administered. The vaccine efficacy is assumed serotype-specific but age-independent as given in Table 1.1. The subfigures (a)–(d) correspond to the CRS (a)–(d) respectively.

Additionally Dengvaxia is fairly effective against both of these serotypes, with an efficacy of nearly 72% for DENv3 and an even higher efficacy of almost 77% for DENv4. From the graph it can be seen that the higher efficacy for DENv4 leads to a lower lifetime expected risk at almost all vaccination ages. An exception to this are vaccination ages below approximately 16 months. Van Panhuis et al. [119] have shown that the rate at which maternal antibodies for DENv4 are decaying is slightly slower than for DENv3, so that at these young vaccination ages the higher risk of vaccinating unsuccessfully outweighs the higher efficacy and thus leads to a slightly higher lifetime expected risk for DENv4 than for DENv3. DENv4 therefore shows the importance of administering vaccinations only once maternal antibodies have decayed enough for vaccination to be successful in most targeted individuals. Once this is the case a higher efficacy will always lead to a lower lifetime expected risk for serotypes with a similar effective reproduction number as one would expect. By considering DENv1 it can be seen that this is even true if the effective reproduction number is slightly higher with a value of approximately 4.7. The effective reproduction number for DENv2 is much lower than for the remaining serotypes and with an efficacy of 43% the vaccine is least effective against DENv2. From the graph it can be seen that the low efficacy for DENv2 leads to a very flat lifetime expected risk curve and to the highest lifetime expected risk by far at young ages even though the low effective reproduction number corresponds to fewer overall cases without the use of vaccination. However, the higher efficacy of Dengvaxia for the other three serotypes, particularly for DENv3 and DENv4 means that many natural infections with these serotypes can be prevented if vaccination is carried out before the disease can spread. Once vaccination takes place in adults above the age of 27 years the lifetime expected risk due to DENv2 is in fact lower than for DENv1. Once the vaccination age increases even further to above 50 years DENv3 also poses a higher risk than DENv2. The vaccination against DENv1, DENv3 and DENv4 at higher ages is taking place after the disease spread and cannot prevent many infections. The lifetime expected risk cannot be significantly reduced if vaccination takes place too late in life and vaccination against DENv1, DENv3 and DENv4 is thus best carried out at young ages of 31, 85 and 42 months respectively. On the other hand, there are in general fewer natural DENv2 infections with a higher average age of infection since the effective reproduction number is very low. Additionally the decay of maternal antibodies against DENv2 is much slower than for the remaining serotypes [119] so that it is best to vaccinate later in life. The optimal vaccination age for DENv2 is 311 months, i.e. just under 26 years.

Next consider CRS (b) as shown in Figure 4.1b. From the graph it is apparent that the lifetime expected risk decreases as the vaccination age increases. This is in fact true even for very high ages so that vaccination in this case is not recommended. In the considered region there is just a single serotype in circulation, so that a natural infection without prior vaccination can only be a primary infection and therefore free of risk. In the absence of vaccination there is consequently zero lifetime expected risk. However, if vaccination is given the natural infection can in fact be a post-primary infection and thus the lifetime expected risk is non-zero. The higher the number of individuals who had a natural infection prior to the vaccination the lower the additional risk is due to post-vaccine infections. The lifetime expected risk therefore decreases with an increase in vaccination age. In fact from the graph it can be seen that DENv2 stands out with the highest lifetime expected risk, whereas the remaining three serotypes have a similar risk particularly at ages above 120 months (10 years). This higher risk due to DENv2 is caused at least to some extent by the low efficacy for this serotype. Vaccination is more likely to be effective against any of the other serotypes so that if only DENv2 is endemic in the area there is a high chance of a post-vaccine infection with DENv2.

Heterologous secondary infections have been found to prevent tertiary and quaternary infections from causing clinical disease [53, 54, 115] so that many recent models assume secondary infections to confer permanent cross-immunity [33, 90]. The corresponding scenarios CRS (c) and CRS (d) for risky and risk-free primary infections can be seen in Figures 4.1c and 4.1d respectively. From the lifetime expected risk curves of DENv1, DENv3, and DENv4 for CRS (c) it can be seen that the observations relating to the effect of different efficacies still apply. However, DENv2 with a low effective reproduction number and low efficacy leads to a lifetime expected risk that at young vaccination ages is very similar to the remaining three serotypes and to the lowest lifetime expected risk for vaccination ages above 240 months (20 years). While the lifetime expected risk due to any of the serotypes is lower for CRS (c) and CRS (d) than for the scenarios with risky post-secondary infections, this difference is most pronounced for DENv2.

For older vaccination ages DENv2 poses a low risk compared to the other serotypes. This is due to different effective reproduction numbers. The high effective reproduction numbers of the other serotypes will have already led to those serotypes spreading before vaccination at high ages and vaccination will therefore have significantly less effect at old age for these serotypes. At younger ages the lifetime expected risk for all serotypes are fairly similar which is caused by

the combination of the low effective reproduction number for DENv2 and the high efficacy for the remaining serotypes. On one hand, since the effective reproduction number means that the average age of infection for DENv2 is relatively high, DENv2 has not spread at young ages. On the other hand, since the vaccine is more likely to be effective against the other serotypes, particularly against DENv3 and DENv4, vaccinating at young ages leads to a higher chance of an infection with DENv2 occurring after successful vaccination against at least two of the other serotypes. Therefore the infection is more likely to be asymptomatic and free of risk.

If DENv3 or DENv4 are in circulation the higher efficacy results in more prevented cases at young vaccination ages, so that the lifetime expected risk is similarly low. For DENv1 the combination of the low efficacy and the high effective reproduction number means that vaccination needs to take place as soon as possible to prevent the disease from spreading and will have far less effect later on. For CRS (c) the optimal vaccination age for all four serotypes is therefore very low and lies between 22 and 42 months. This is particularly interesting in the case of DENv2 with an optimal vaccination age of 311 months in CRS (a) when all infections are risky, and can be explained by considering the decay of maternal antibodies and the low efficacy. CRS (a) means that all infections are symptomatic and the vaccine needs to prevent an infection with DENv2 to reduce the risk. However, since the efficacy for DENv2 is already low and further decreased at younger ages due to the slow decay of maternal antibodies it is best to vaccinate late. In CRS (c) it is sufficient to successfully vaccinate against two of the other serotypes which is achievable at young ages so that the optimal vaccination age in this case depends less on DENv2 than on the remaining serotypes.

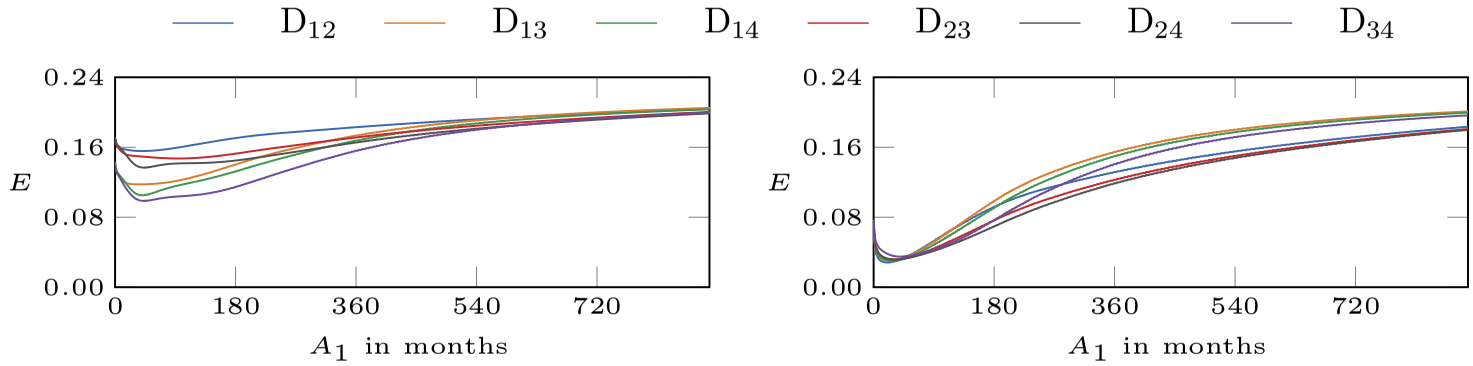
For CRS (d) vaccination is again not recommended for the same reasons as in the case of CRS (b). Additionally from Figure 4.1d it can be seen that the assumption of asymptomatic tertiary and quaternary infections in the case of risk-free primary infections has a similar effect on the lifetime expected risk of DENv2 as in the case of risky primary infections. However, the higher chance of a possible post-vaccine infection for DENv2 due to the lower efficacy of this serotype again leads to DENv2 posing the highest lifetime expected risk if vaccination is carried out.

By studying an endemic area with a single serotype in circulation it can therefore be seen that efficacy, effective reproduction number, and decay of maternal antibodies all significantly influence the optimal vaccination ages, particularly when all infections are considered equally risky. For asymptomatic third and fourth infections the differences are much less relevant and optimal vaccination

ages are similar for all serotypes. Vaccination is not recommended in an endemic region with only one serotype when primary infections are risk-free as one would intuitively expect.

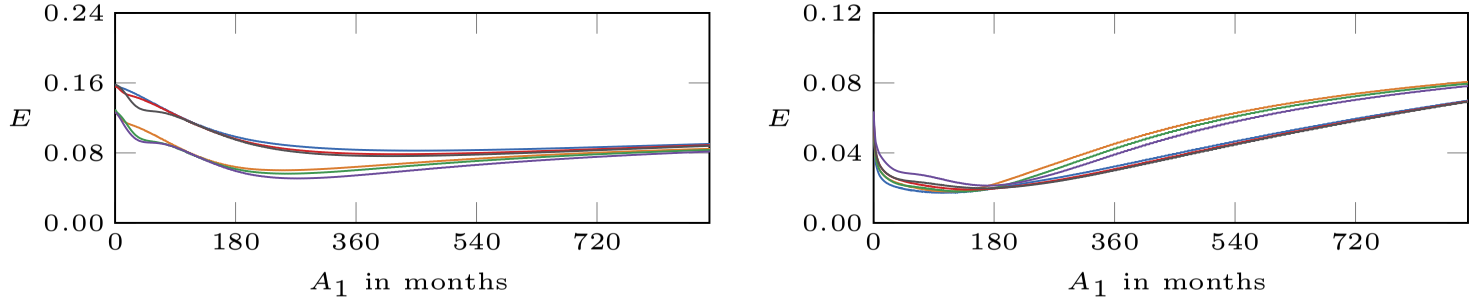
Next an endemic region with two co-circulating serotypes is studied. The results for any combination of two coexisting serotypes are presented in Figure 4.2 where again the subfigures are numbered according to the CRS they correspond to. Again successful vaccination can be understood as a silent infection so that even though there are only two serotypes present tertiary and quaternary infections are possible.

In CRS (a) all infections are equally likely to require hospital treatment. From Figure 4.2a it can be seen that the optimal vaccination ages in this scenario are mostly relatively low, between 36 and 44 months. The only exception is the combination DENv23 in which case vaccination should take place at 95 months. However, the lifetime expected risk due to DENv23 is very flat in general and near-optimal vaccination could be achieved at similarly early vaccination ages as for the remaining serotype combinations. In fact, any combination including DENv2 leads to a relatively flat lifetime expected risk curve. For young vaccination ages these combinations are clearly distinguishable since they lead to a higher lifetime expected risk than combinations without DENv2. The lifetime expected risk for two serotypes is much higher in general than for a single serotype. Further in CRS (b) and CRS (d) vaccination is in fact recommended for two coexisting serotypes. However, the optimal vaccination ages in CRS (b) are much higher and more varied than in CRS (a). This increase in comparison to risky primary infections can be explained intuitively since vaccination before the first infection is in fact not necessary if the infection does not pose any risk. It is therefore better to wait with vaccination until after the primary infection occurred to make sure that less vaccinated individuals are still protected by maternal antibodies. Again the presence or absence of DENv2 seems to have a great influence due to the slow decay rate of maternal antibodies. Combinations that include this serotype require vaccination at ages between 411 and 452 months (approximately 34 and 37.5 years), while those without DENv2 require vaccination between 249 and 271 months (approximately 21 and 22.5 years). The reason for this is the high risk of an infection with DENv2 occurring after vaccination since the vaccine is least effective against this serotype and maternal antibodies decay slowly and thus further reduce the effectiveness at young ages.




(a) The optimal vaccination ages for DENv12, DENv13, DENv14, DENv23, DENv24 and DENv34 are 42, 36, 42, 95, 44 and 44 months respectively.

(c) The optimal vaccination ages for DENv12, DENv13, DENv14, DENv23, DENv24 and DENv34 are 22, 25, 28, 31, 31 and 37 months respectively.




(b) The optimal vaccination ages for DENv12, DENv13, DENv14, DENv23, DENv24 and DENv34 are 452, 249, 258, 423, 411 and 271 months respectively.

(d) The optimal vaccination ages for DENv12, DENv13, DENv14, DENv23, DENv24 and DENv34 are 122, 122, 125, 145, 166 and 170 months respectively.

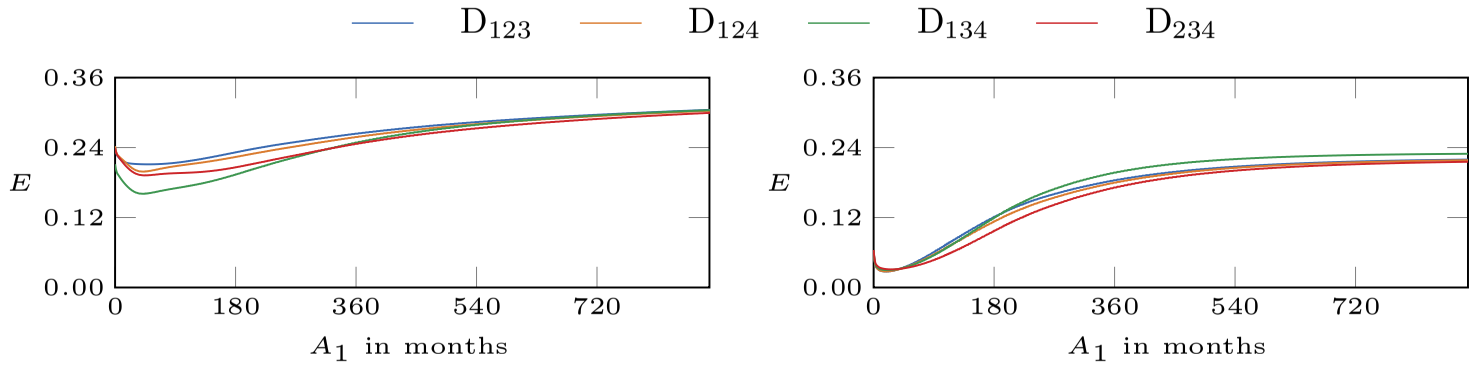
Figure 4.2: The lifetime expected risk $E$ of hospitalisation in an endemic area where two serotypes coexist as a function of age $A_1$ at which the first vaccine dose is administered. The vaccine efficacy is assumed serotype-specific but age-independent as given in Table 1.1. The subfigures (a)–(d) correspond to the CRS (a)–(d) respectively.

In the case of asymptomatic tertiary and quaternary infections (CRS (c) and CRS (d)) the low effective reproduction number of DENv2 actually leads to a lower risk if vaccination takes place late for a single serotype. From Figures 4.2c and 4.2d this can also be observed for any combination with two coexisting serotypes when DENv2 is present. Similarly to the case of a single serotype the optimal vaccination ages for CRS (c) are less varied for the different combinations and lower than in the case of CRS (a). The optimal age lies between 22 and 37 months. For CRS (d), i.e. when only secondary infections are risky, the optimal vaccination ages lie between 122 and 170 months. Again the increase in comparison to CRS (c) is due to primary infections not being targeted. However, in addition to that vaccination is now only effective if it is administered before a secondary infection. The optimal vaccination ages are therefore lower for CRS (d) than for CRS (b).

For two coexisting serotypes it can therefore be said that vaccination ages highly depend on whether primary infections are risky independent of whether PCI is considered. Additionally if two heterologous infections do not confer PCI the presence or absence of DENv2 greatly impacts the vaccination age and the lifetime expected risk. On the other hand in CRS (c) there is very little variance in the optimal vaccination ages for the different serotype combinations.

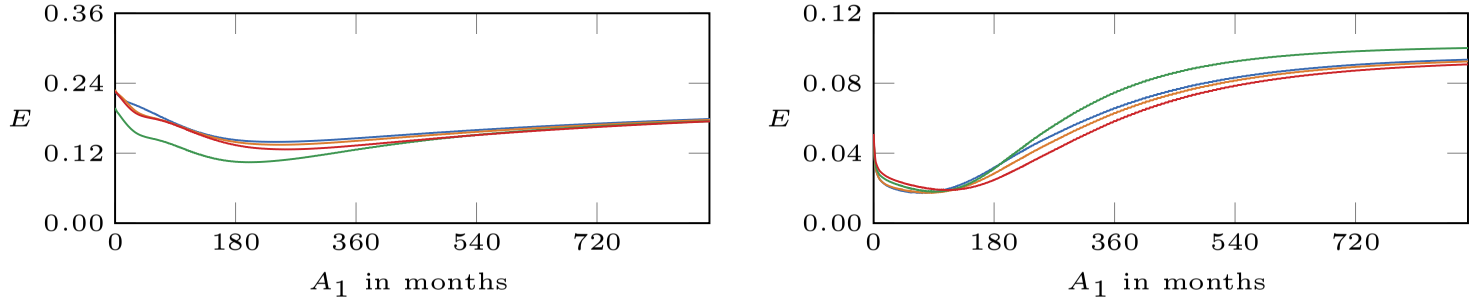
For three coexisting serotypes in an endemic region as presented in Figure 4.3 most of the observations for two co-circulating serotypes apply as well. The combination of DENv134 behaves similarly to the combinations with two serotypes that do not include DENv2 in any CRS. However, the optimal vaccination ages for three coexisting serotypes are actually slightly lower than for the corresponding cases with two serotypes. An additional serotype can be understood to increase the overall effective reproduction number for dengue. The lower optimal vaccination ages for three serotypes are in fact to be expected since the average age of infection is reduced and therefore vaccination needs to be administered sooner.

The results for all dengue serotypes coexisting are shown in Figure 4.4. In this case the optimal vaccination ages are 44 months for all infections being equally risky (CRS (a)), 192 months for risk-free primary infections but risky third and fourth infections (CRS (b)), 16 months for risky primary infections but asymptomatic tertiary and quaternary infections (CRS (c)), and 64 months if only secondary infections are considered risky (CRS (d)). Therefore the introduction of the last serotype again tends to decrease the optimal vaccination age in every scenario. The differences in optimal vaccination age between CRS (a)–(d) are similar to before.




(a) The optimal vaccination ages for DENv123, DENv124, DENv134 and DENv234 are 50, 42, 42 and 46 months respectively.

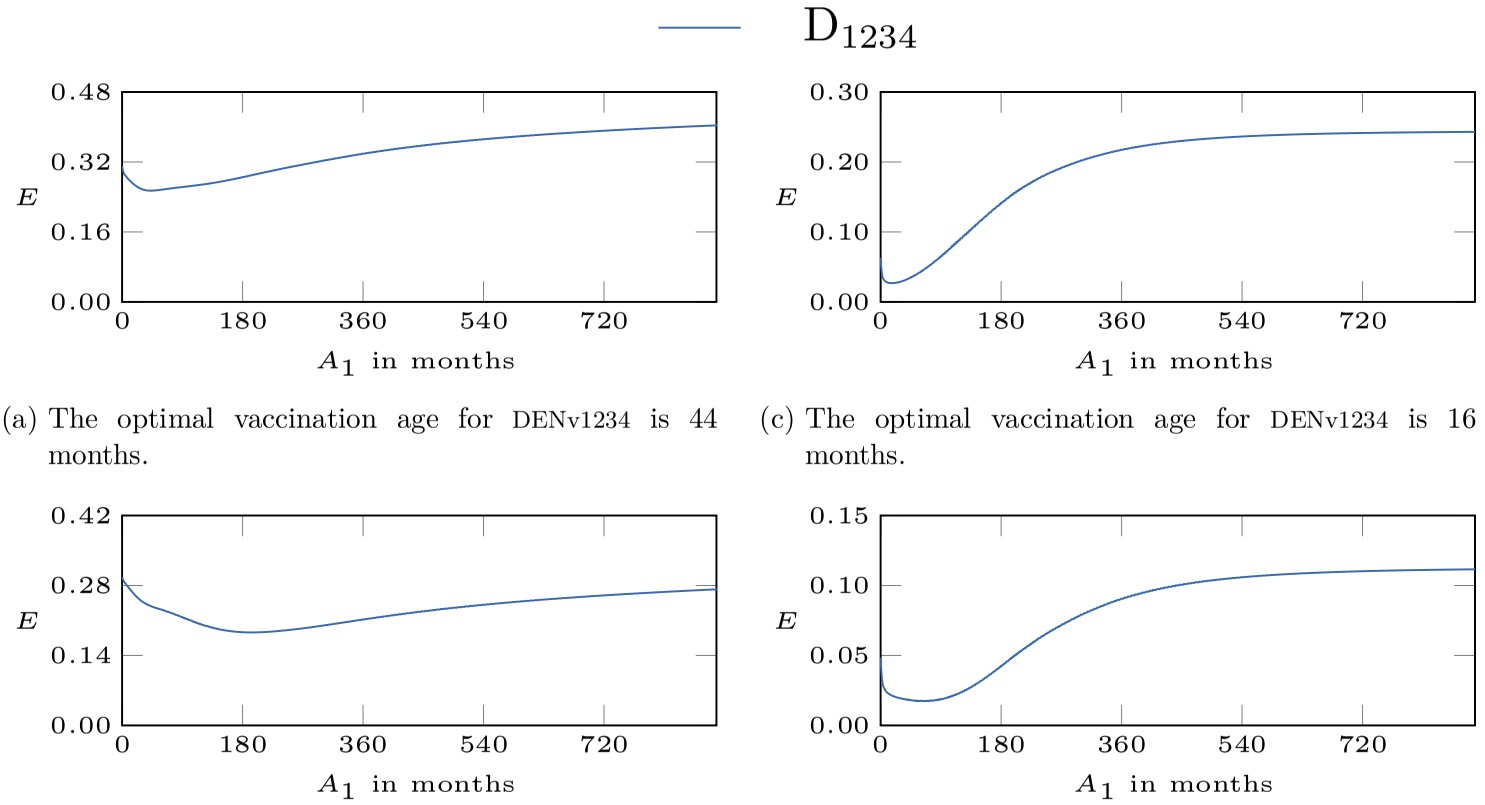
(c) The optimal vaccination ages for DENv123, DENv124, DENv134 and DENv234 are 19, 19, 22 and 25 months respectively.




(b) The optimal vaccination ages for DENv123, DENv124, DENv134 and DENv234 are 236, 245, 199 and 254 months respectively.

(d) The optimal vaccination ages for DENv123, DENv124, DENv134 and DENv234 are 73, 80, 92 and 116 months respectively.

Figure 4.3: The lifetime expected risk $E$ of hospitalisation in an endemic area where three serotypes coexist as a function of age $A_1$ at which the first vaccine dose is administered. The vaccine efficacy is assumed serotype-specific but age-independent as given in Table 1.1. The subfigures (a)–(d) correspond to the CRS (a)–(d) respectively.




(a) The optimal vaccination age for DENv1234 is 44 months.

(c) The optimal vaccination age for DENv1234 is 16 months.

(b) The optimal vaccination age for DENv1234 is 192 months.

(d) The optimal vaccination age for DENv1234 is 64 months.

Figure 4.4: The lifetime expected risk $E$ of hospitalisation in an endemic area where all four serotypes coexist as a function of age $A_1$ at which the first vaccine dose is administered. The vaccine efficacy is assumed serotype-specific but age-independent as given in Table 1.1. The subfigures (a)–(d) correspond to the CRS (a)–(d) respectively.

Table 4.2: The optimal vaccination age $A_1$ in months which minimises the lifetime expected risk $E$ of hospitalisation for all CRSs. The vaccine efficacy is assumed serotype-specific but age-independent as given in Table 1.1. '–' represents cases in which vaccination is not recommended, i.e. when $A_1$ was found to be above a reasonable age for humans.

| | CRS (a) | | CRS (b) | | CRS (c) | | CRS (d) | |
|---|---|---|---|---|---|---|---|---|
| | $A_1$ | $E_{\times 10^{-2}}$ | $A_1$ | $E_{\times 10^{-2}}$ | $A_1$ | $E_{\times 10^{-2}}$ | $A_1$ | $E_{\times 10^{-2}}$ |
| DENv1 | 31 | 6.18 | – | 0.00 | 22 | 2.16 | – | 0.00 |
| DENv2 | 311 | 9.02 | – | 0.00 | 31 | 2.60 | – | 0.00 |
| DENv3 | 85 | 5.46 | – | 0.00 | 36 | 2.32 | – | 0.00 |
| DENv4 | 42 | 4.31 | – | 0.00 | 42 | 1.83 | – | 0.00 |
| DENv12 | 42 | 15.57 | 452 | 8.26 | 22 | 2.82 | 122 | 1.72 |
| DENv13 | 36 | 11.76 | 249 | 6.01 | 25 | 3.05 | 122 | 1.79 |
| DENv14 | 42 | 10.51 | 258 | 5.63 | 28 | 2.98 | 125 | 1.78 |
| DENv23 | 95 | 14.72 | 423 | 7.85 | 31 | 3.18 | 145 | 1.90 |
| DENv24 | 44 | 13.67 | 411 | 7.63 | 31 | 3.15 | 166 | 1.97 |
| DENv34 | 44 | 9.86 | 271 | 5.08 | 37 | 3.50 | 170 | 2.12 |
| DENv123 | 50 | 21.12 | 236 | 13.94 | 19 | 2.73 | 73 | 1.73 |
| DENv124 | 42 | 19.88 | 245 | 13.45 | 19 | 2.75 | 80 | 1.73 |
| DENv134 | 42 | 16.07 | 199 | 10.45 | 22 | 2.97 | 92 | 1.80 |
| DENv234 | 46 | 19.22 | 254 | 12.65 | 25 | 3.10 | 116 | 1.89 |
| DENv1234 | 44 | 25.44 | 192 | 18.61 | 16 | 2.68 | 64 | 1.73 |

All optimal vaccination ages together with the minimal lifetime expected risk for the discussed scenarios are presented in Table 4.2. From the table it can be seen that the minimal lifetime expected risk increases with every additional serotype in CRS (a). In CRS (c) this is only true if an additional serotype is added to an endemic area with a single serotype in circulation, otherwise the risk decreases. This is not very intuitive and probably caused due to a combination of different effects. In CRS (c) it is sufficient to successfully vaccinate against any two serotypes before an infection occurs independent of which or how many serotypes are in circulation. The higher the efficacy against non-endemic serotypes the lower the lifetime expected risk will therefore be. Further the reduction in average age of infection might mean that possible risky infections occur at lower risk ages and therefore the risk decreases as more serotypes are present. Similar differences can be observed between CRS (b) and CRS (d) for areas with more than one serotype in circulation. However, there are some cases in CRS (d) that lead to an increase in lifetime expected risk when an additional serotype is added. In particular if serotype DENv1 coexists with serotype DENv2 and either DENv3 or DENv4 is added the lifetime expected risk increases.

In summary it can be said that for a constant, serotype-specific vaccine efficacy the vaccination ages depend significantly on the serotypes present. The optimal vaccination age decreases as the number of serotypes increases since more serotypes lead to a lower average age of infection. However, in general the assumption of risk-free primary infections leads to an increase in vaccination ages since primary infections do not need to be targeted. The only exception to this is the case of a single serotype where vaccination is not recommended at all. Assuming secondary infections to result in PCI leads to a decrease in optimal vaccination ages which is caused by the vaccination being unnecessary once a secondary infection has occurred. Additionally the differences between effective reproduction number, vaccine efficacy and decay of maternal antibodies significantly influence the lifetime expected risk caused by a specific serotype combination.

### Age-Dependent Vaccine Efficacy

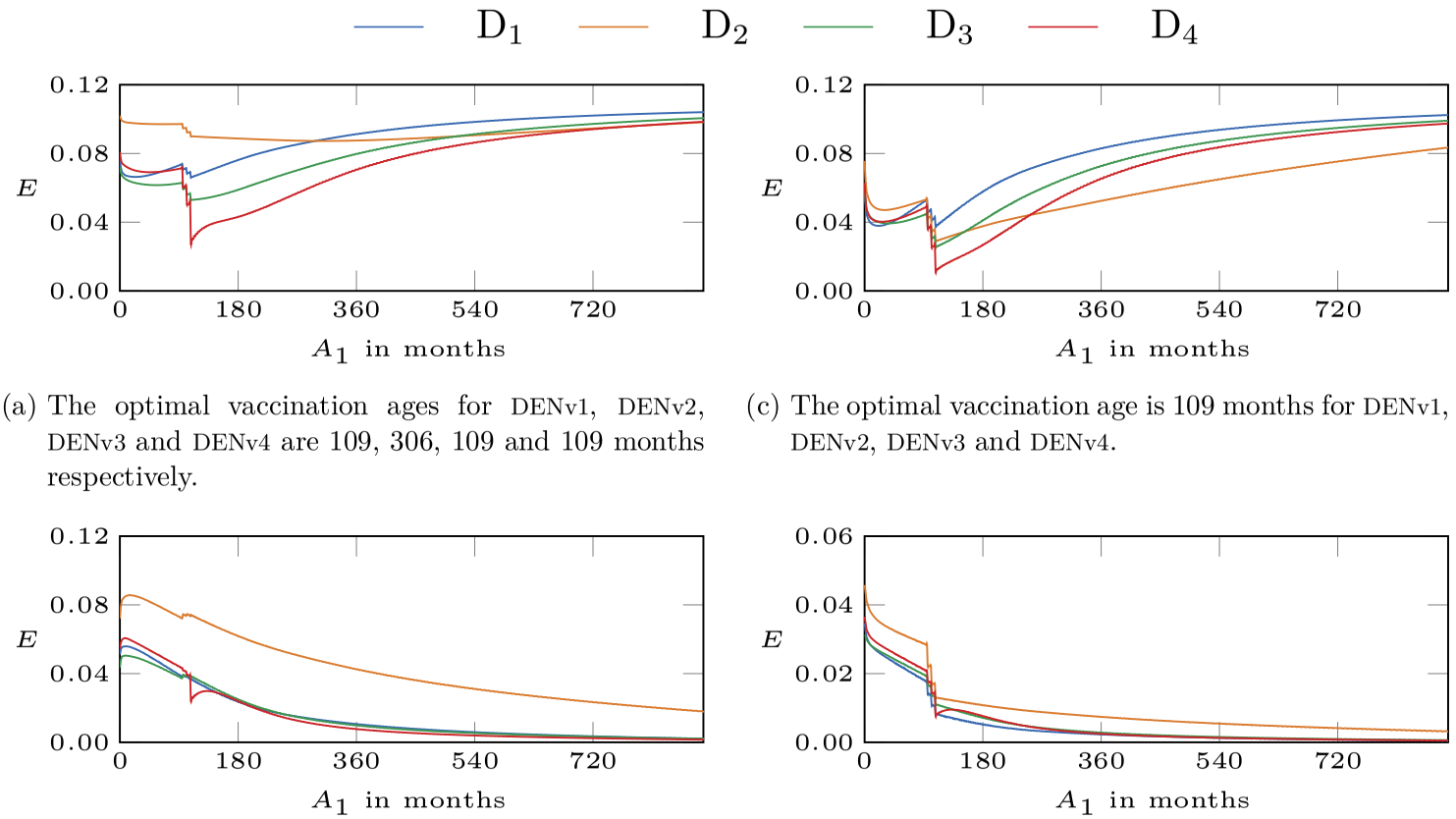
Hadinegoro et al. [66] and Capeding et al. [32] found that the effectiveness of Dengvaxia is not only different for each of the serotypes but that it also depends on the age of the recipient. The age-dependent efficacies for each of the serotypes

Table 4.3: The optimal vaccination age $A_1$ in months which minimises the lifetime expected risk $E$ of hospitalisation for all CRSs. The vaccine efficacy is assumed serotype-specific and age-dependent as given in Table 1.1. '–' represents cases in which vaccination is not recommended, i.e. when $A_1$ was found to be above a reasonable age for humans.

| | CRS (a) | | CRS (b) | | CRS (c) | | CRS (d) | |
|---|---|---|---|---|---|---|---|---|
| | $A_1$ | $E_{\times 10^{-2}}$ | $A_1$ | $E_{\times 10^{-2}}$ | $A_1$ | $E_{\times 10^{-2}}$ | $A_1$ | $E_{\times 10^{-2}}$ |
| DENv1 | 109 | 6.61 | – | 0.00 | 109 | 3.75 | – | 0.00 |
| DENv2 | 306 | 8.73 | – | 0.00 | 109 | 2.89 | – | 0.00 |
| DENv3 | 109 | 5.29 | – | 0.00 | 109 | 2.55 | – | 0.00 |
| DENv4 | 109 | 2.84 | – | 0.00 | 109 | 1.17 | – | 0.00 |
| DENv12 | 109 | 15.61 | 440 | 7.97 | 109 | 5.38 | 109 | 1.33 |
| DENv13 | 109 | 11.90 | 249 | 5.77 | 109 | 5.30 | 109 | 1.38 |
| DENv14 | 109 | 9.45 | 249 | 4.99 | 109 | 4.33 | 109 | 1.24 |
| DENv23 | 109 | 14.29 | 417 | 7.57 | 109 | 4.20 | 135 | 1.45 |
| DENv24 | 109 | 11.84 | 389 | 7.17 | 109 | 3.36 | 170 | 1.54 |
| DENv34 | 109 | 8.13 | 267 | 4.54 | 109 | 3.34 | 173 | 1.64 |
| DENv123 | 109 | 20.90 | 240 | 13.43 | 19 | 5.28 | 109 | 1.53 |
| DENv124 | 109 | 18.45 | 240 | 12.48 | 16 | 5.20 | 109 | 1.36 |
| DENv134 | 109 | 14.74 | 203 | 9.49 | 16 | 5.24 | 109 | 1.40 |
| DENv234 | 109 | 17.13 | 254 | 11.78 | 109 | 4.36 | 122 | 1.46 |
| DENv1234 | 109 | 23.74 | 196 | 17.33 | 16 | 5.20 | 109 | 1.58 |

according to [66] are presented in Table 1.1. In this section the effect of an age-dependent efficacy when the risk of an infection is considered to be hospitalisation will be discussed. The resulting optimal vaccination age and minimal lifetime expected risk for any combination of serotypes is shown in Table 4.3. For an age-dependent efficacy the graphs obtained are overall similar to those for a constant efficacy. However, the change in efficacy at 9 years of age leads to drops in the lifetime expected risk. This will be discussed in detail for an endemic area with only one serotype in existence but applies similarly to any number of coexisting serotypes. It is also important to note that while the efficacy studies [32, 66] attributed the difference to the age of the recipient per se, Aguiar and Stollenwerk [4] raise the question whether the observed increase in efficacy is in fact correlated with the serostatus rather than the age of the recipient, i.e. they suggest that the vaccine is more effective in seropositive individuals. If this is the case the results for a constant efficacy are more realistic.

The results for an age-dependent efficacy in an endemic region with a single serotype are presented in Figure 4.5 where the subfigures again show the corresponding CRSs. By comparing these results to those for a constant efficacy as shown in Figure 4.1 it can be seen that the overall behaviour of the lifetime expected risk is in fact similar. The main differences, independent of the CRS, are the three drops that occur for $A_1 = 8, 8.5$ and 9 years (96, 102, and 108 months) which are the vaccination ages for which one of the doses is first given in the age group of 9 years or above so that the higher efficacy applies. Additionally one can see that for ages below 8 years the lifetime expected risk is slightly higher due to the lower efficacy in that age-group compared with the constant efficacy in CRS (a), CRS (c) and CRS (d). This is most noticeable for DENv4 since the difference in efficacy is most significant for this serotype. On the other hand, for ages above 9 years where the higher efficacy applies to all three doses the lifetime expected risk is in fact slightly lower. Again these observations are true independently of the assumptions relating to cross-immunity. However, in CRS (b) the lifetime expected risk does not behave in the same way. In this case without vaccination there is no risk. Successful vaccination against any non-endemic serotypes that was unsuccessful against the endemic serotype increases the risk. A lower efficacy is therefore not necessarily causing a higher risk and vice versa. For example, if DENv2 exists instead of dropping the lifetime expected risk increases if a dose is given in the older age-group. This is due to the efficacy for this serotype being low independently of the age-group, but if the vaccine is more effective against the other three serotypes the probability of an infection with DENv2 occurring




(a) The optimal vaccination ages for DENv1, DENv2, DENv3 and DENv4 are 109, 306, 109 and 109 months respectively.

(c) The optimal vaccination age is 109 months for DENv1, DENv2, DENv3 and DENv4.

(b) Vaccination is not recommended for any serotype.

(d) Vaccination is not recommended for any serotype.

Figure 4.5: The lifetime expected risk $E$ of hospitalisation in an endemic area where a single serotype exists as a function of age $A_1$ at which the first vaccine dose is administered. The vaccine efficacy is assumed serotype-specific and age-dependent as given in Table 1.1. The subfigures (a)–(d) correspond to the CRS (a)–(d) respectively.

after vaccination is higher. Therefore the risk increases since there is no risk if vaccination does not take place at all even though the efficacy increases.

The increase in efficacy has a large effect on the optimal vaccination age, particularly for the case of risky primary infections, i.e. CRS (a) and CRS (c). While for a constant efficacy the optimal age is 31, 311, 85 and 42 months for DENv1–4 respectively in CRS (a), for an age-dependent vaccine efficacy the optimal age is almost unchanged for DENv2 with an optimum at 306 months, but it is much higher at 109 months for DENv1, DENv3 and DENv4. In CRS (c) the optimal vaccination ages increase from between 22–42 months to 109 months for all serotypes on their own. Similarly for two coexisting serotypes, where the optimal ages all increase significantly to 109 months. However, for three and four coexisting serotypes in CRS (c) this is only true for the combination DENv234 as can be seen in Table 4.3. The remaining combinations, i.e. combinations of at least three serotypes including DENv1, require vaccination at similarly low ages as for a constant efficacy.

For risk-free primary infections, i.e. CRS (b) and CRS (d), vaccination is still not recommended if only a single serotype exists in an endemic region. For several coexisting serotypes the optimal ages found for a constant efficacy are all 109 months or above and thus the optimal vaccination ages are almost all unchanged in comparison to the case of a constant efficacy similarly to DENv2 in CRS (a). Again the only exceptions to this are combinations of at least three serotypes including DENv1 in CRS (d) in which case the optimal vaccination age is between 64 and 92 months for a constant efficacy, but now actually increases to 109 months.

By considering an age-dependent efficacy in most cases an increase of the optimal vaccination age to 109 months is observed if it is below this age for a constant efficacy. However, for optimal vaccination ages that are above 109 months in the case of a constant efficacy, the assumption has little effect on the optimal vaccination ages obtained. In these cases the lifetime expected risk is slightly lower if efficacy does indeed depend on the age of the recipient. This is due to the higher efficacy in the age-group above 9 years compared to the pooled efficacy.

**Licence Restrictions**

The optimal vaccination ages that were obtained are clearly not all within the permitted age-range for Dengvaxia in Brazil which is 9 to 45 years. In fact in CRS (a) and CRS (c) for a constant efficacy only DENv2 leads to an optimal vaccination age within that range, all other optimal vaccination ages are far below the required 108 months. For an age-dependent efficacy only combinations of three and four serotypes including DENv1 lead to vaccination ages below 108 months. However, in CRS (b) and CRS (d) almost all vaccination ages are within the permitted age-range independently of the assumption relating to efficacy. The exception is again DENv1 coexisting with at least two other serotypes when the vaccine efficacy is assumed constant. In this case the optimal vaccination age is lower than 9 years.The effect of restricting the vaccination ages will therefore be discussed for all cases with an optimal vaccination age below 108 months. The

Table 4.4: The vaccination age $A_1$ in months which lies within the permitted age-range for the vaccine and minimises the lifetime expected risk $E$ of hospitalisation. The percentage increase from the optimal lifetime expected risk $\delta_E\%$ is given for any case in which the optimal vaccination age lies outwith the permitted age-range of Dengvaxia. For cases in which vaccination is not recommended the minimal lifetime expected risk is zero, so that the percentage increase is given by $\infty$. The vaccine efficacy is assumed serotype-specific but age-independent as given in Table 1.1.

| | CRS (a) | | CRS (b) | | CRS (c) | | CRS (d) | |
|---|---|---|---|---|---|---|---|---|
| | $A_1$ | $\delta_E\%$ | $A_1$ | $\delta_E\%$ | $A_1$ | $\delta_E\%$ | $A_1$ | $\delta_E\%$ |
| DENv1 | 109 | 12 | 538 | $\infty$ | 109 | 96 | 531 | $\infty$ |
| DENv2 | 311 | – | 539 | $\infty$ | 109 | 34 | 539 | $\infty$ |
| DENv3 | 109 | 1 | 538 | $\infty$ | 109 | 30 | 531 | $\infty$ |
| DENv4 | 109 | 15 | 538 | $\infty$ | 109 | 37 | 531 | $\infty$ |
| DENv12 | 109 | 4 | 452 | – | 109 | 118 | 122 | – |
| DENv13 | 109 | 6 | 249 | – | 109 | 101 | 122 | – |
| DENv14 | 109 | 13 | 258 | – | 109 | 90 | 125 | – |
| DENv23 | 109 | <1 | 423 | – | 109 | 58 | 145 | – |
| DENv24 | 109 | 4 | 411 | – | 109 | 47 | 166 | – |
| DENv34 | 109 | 6 | 271 | – | 109 | 38 | 170 | – |
| DENv123 | 109 | 3 | 236 | – | 109 | 169 | 109 | 12 |
| DENv124 | 109 | 6 | 245 | – | 109 | 147 | 109 | 5 |
| DENv134 | 109 | 8 | 199 | – | 109 | 126 | 109 | 3 |
| DENv234 | 109 | 2 | 254 | – | 109 | 80 | 116 | – |
| DENv1234 | 109 | 5 | 192 | – | 109 | 200 | 109 | 22 |

resulting vaccination ages which are ideal under the licence restriction together with the percentage increase from the minimal lifetime expected risk are presented in Table 4.4 for a constant vaccine efficacy. For risk-free primary infections (CRS (b) and CRS (d)) and a single serotype in circulation vaccination is not actually recommended since the lifetime expected risk is zero if no vaccination takes place. In all other cases which lead to a vaccination age below 108 months the optimal vaccination age is 109 months if it is restricted according to the licence. Due to the nature of the objective function and the inaccuracy of the numerical integration this can be understood as exactly 9 years, i.e. as soon as possible after the optimal age. Depending on the CRS the percentage increase varies significantly. For DENv23 in CRS (a) with a constant efficacy it is less than 1%, on the other hand if all four serotypes coexist in CRS (c) it is as high as 200%. The increase from the minimal lifetime expected risk is in general much higher for CRS (c) than for CRS (a), CRS (b) and CRS (d) if vaccination is recommended.

For an age-dependent efficacy there are only four cases that resulted in an optimal vaccination age below 9 years (DENv123, DENv124, DENv134 and DENv1234 in CRS (c)) so that a table for this case is omitted. Under licence restriction all of them require vaccination at 109 months and the percentage increase from the minimal lifetime expected risk is 23%, 7%, 5% and 28% respectively.

Limiting the vaccination ages to the restriction of the licence therefore has a great impact on the achievable reduction of hospitalisation risk. Particularly if secondary infections confer PCI and primary infections are risky much better results could be achieved if vaccination were to be permitted in younger children. However, if the efficacy does indeed depend on the age of the recipient the restriction has hardly any effect.

### 4.4.2 Minimising the Risk of Lethality

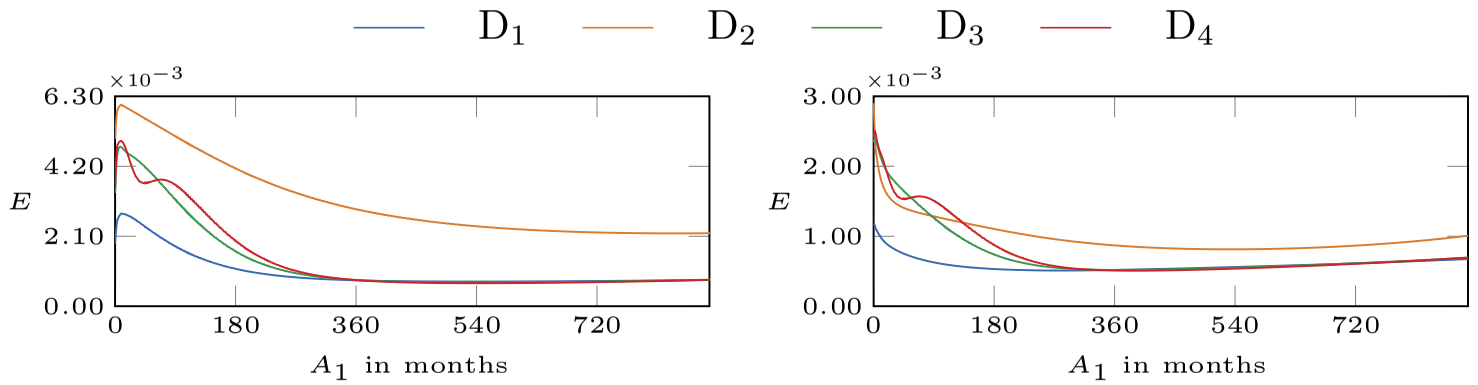
Instead of looking at the risk of requiring hospital treatment the lethality due to an infection with dengue can be considered. The lethality risk function $R^L(a)$ was found in the previous chapter (cf. Equation (3.30)). There is a peak of lethality at young ages as well as an increase in risk at older ages. The more people get treated for dengue in hospital the more will die of a dengue infection so that we might expect there to be a high degree of correlation between the risk of hospitalisation and lethality. The risk of lethality is always significantly lower than that of hospitalisation. However, while the risk of hospitalisation at old ages reaches a similar level to its peak for children, the risk of lethality at the age of 75 years is approximately fourfold the risk of death for young children and at

later ages this risk is much larger. Of particular interest for this risk will thus be the influence of the high risk at old ages on the optimal vaccination age. Initially the vaccine efficacy is again assumed to be age-independent and subsequently the effect of an age-dependent efficacy will be discussed. For scenarios with an optimal age out with the permitted age range the licence restriction is applied.

### Constant Vaccine Efficacy

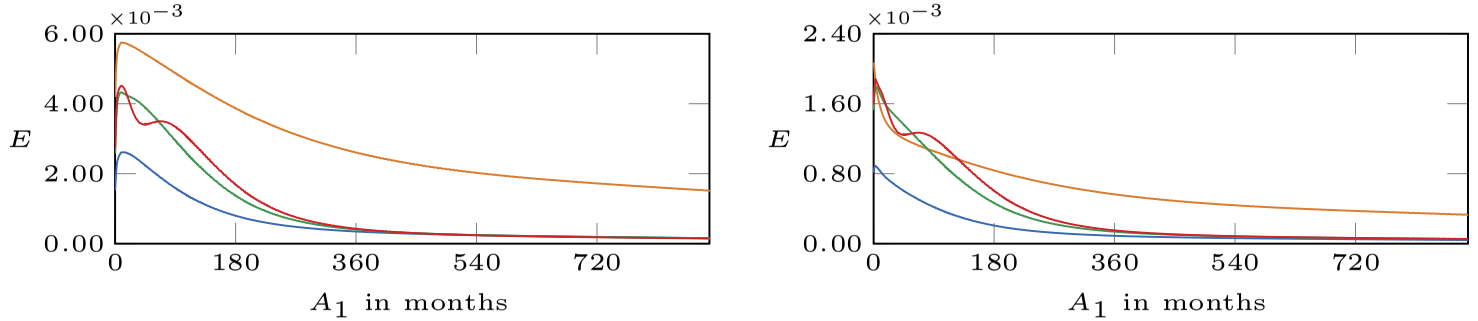
Again begin by considering an endemic region with only one serotype in circulation in order to understand the differences between the four serotypes. The results are presented in Figure 4.6 where the subfigures (a)–(d) again correspond to CRS (a)–(d) respectively. Note that the tetravalence of the vaccine is responsible for the possibility of an infection being a secondary, tertiary or quaternary infection depending on how many serotypes an individual was successfully vaccinated against.

By considering all infections to be equally risky as shown in Figure 4.6a, one can see that the very high risk at older ages for lethality compared to hospitalisation has a significant impact on the lifetime expected risk and the optimal vaccination age. The optimal vaccination age for any of the four serotypes is very high with those for DENv1, DENv3 and DENv4 between 532 and 544 months and that for DENv2 even higher at 840 months. Clearly at these high vaccination ages only very few infections will be prevented as most will have already occurred earlier in life. Vaccination will result in a higher average age of infection and since the risk of lethality increases drastically at older ages it is reasonable that this effect needs to be kept small. Due to the very high risk at older ages it is therefore better to prevent infections that occur at those high-risk ages rather than infections in younger individuals so that the average age is not affected too much while some high-risk infections can still be prevented. Considering this it is not surprising that the highest lifetime expected risk for any vaccination age is caused by DENv2 and the lowest by DENv1. DENv2 has the lowest effective reproduction number so that the average age of infection is highest without vaccination and therefore more infections with this serotype occur at high-risk ages even though the low effective reproduction number corresponds to fewer infections overall. Vaccination reduces the effective reproduction number and increases the average age of infection so that those infections that do occur are likely associated with an even higher risk and thus independent of vaccination age the risk due to DENv2 is far higher than that of the remaining serotypes. DENv1 has the highest effective reproduction number and thus the lowest average age of infection resulting in a




(a) The optimal vaccination ages for DENv1, DENv2, DENv3 and DENv4 are 532, 840, 544 and 540 months respectively.

(c) The optimal vaccination ages for DENv1, DENv2, DENv3 and DENv4 are 278, 537, 368 and 390 months respectively.




(b) Vaccination is not recommended for any serotype.

(d) Vaccination is not recommended for any serotype.

Figure 4.6: The lifetime expected risk $E$ of lethality in an endemic area where a single serotype exists as a function of age $A_1$ at which the first vaccine dose is administered. The vaccine efficacy is assumed serotype-specific but age-independent as given in Table 1.1. The subfigures (a)–(d) correspond to the CRS (a)–(d) respectively.

lower lifetime expected risk than any other serotype. DENv3 and DENv4 cause a similar lifetime expected risk at most vaccination ages since they have a similar effective reproduction number. Considering that vaccination only takes place after most infections will have occurred the efficacy is less relevant than if the risk of hospitalisation is minimised. However, due to the high efficacy for DENv3 and DENv4 some infections at old ages can be prevented for older vaccination ages and the lifetime expected risk is similar to that of DENv1 at these high vaccination ages.

If primary infections are assumed to be risk-free, as shown in Figure 4.6b, vaccination is again not recommended. The reasons for this are the same as discussed in the case of hospitalisation, i.e. without vaccination the natural infection has to be a primary infection and is free of risk. However, if vaccination takes place the highest lifetime expected risk is caused by DENv2 due to the higher average age of infection compared to the other serotypes as well as the low efficacy. Independent of the vaccination age the lifetime expected risk is slightly lower than in CRS (a) since at least some infections will be primary infections due to the vaccine being imperfect or because they take place before the vaccine is administered.

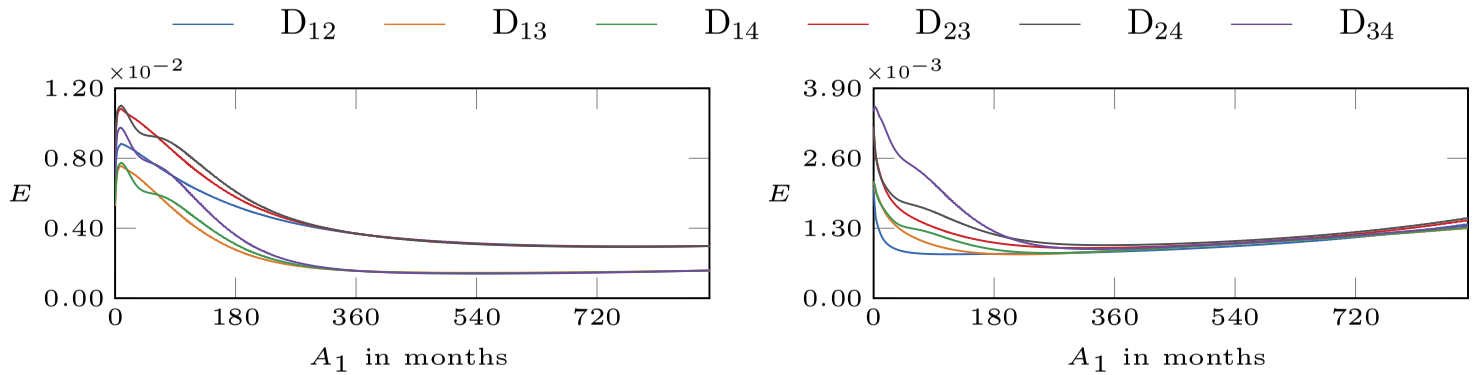
CRS (c) is shown in Figure 4.6c. Post-secondary infections in this scenario are risk-free and thus the lifetime expected risk is much lower than in CRS (a). The optimal vaccination ages are also reduced in comparison to CRS (a) to between 278 and 390 months for DENv1, DENv3 and DENv4 and 537 months for DENv2. Again DENv2 requires vaccination later than the other serotypes due to the higher average age of infection. However, the lifetime expected risk due to this serotype is no longer the highest at any vaccination age. If the vaccine is given to individuals below the age of 7.5 years the risk due to DENv2 is smaller than that due to DENv3 or DENv4 and even at older ages the risk is not significantly higher. The reason for this is similar to the smaller difference in lifetime expected risk in the case of hospitalisation. In particular, if vaccination is successful against any two serotypes no subsequent infection will be risky. Consequently there is now a trade-off between increasing the average age of infection and ensuring infections are risk-free due to successful vaccination against any two serotypes.

In CRS (d) as shown in Figure 4.6d, vaccination is intuitively not recommended since without it the risk will be zero. If vaccination takes place the lifetime expected risk for each of the serotypes behaves similarly to CRS (c) since successful vaccination against any two serotypes will result in risk-free subsequent infections.

By considering a single serotype in circulation it can therefore be seen that if the risk of lethality is minimised the most relevant factor is the average age

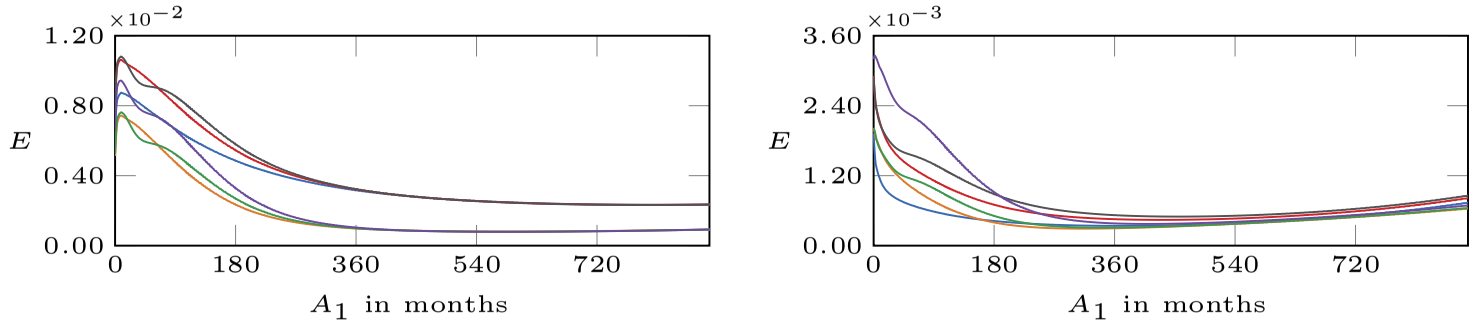
of infection which is closely related to the effective reproduction number. The lower the effective reproduction number the higher the average age of infection and therefore the lifetime expected risk. In order to keep the increase in average age of infection minimal the optimal vaccination age is fairly high in CRS (a) and CRS (c) where vaccination is recommended. Essentially vaccination only takes place after most infections have occurred to prevent only those at high ages. Consequently the efficacy for a specific serotype is less relevant than in the case of hospitalisation but if the efficacy is high more of the high-risk infections can be prevented.

The results for two and three coexisting serotypes for the risk of lethality are presented in Figures 4.7 and 4.8 respectively where again the subfigures correspond to the four CRSs. Since there are several serotypes in circulation vaccination is now recommended in CRS (b) and CRS (d). As for a single serotype in CRS (a) the optimal vaccination ages are very high for all combinations and even higher if DENv2 is endemic due to its low effective reproduction number. The optimal vaccination ages in CRS (b) are in fact very similar to those in CRS (a). This is to be expected since vaccination in the case of lethality is ideal after most infections at relatively low-risk ages occurred but before those at very older ages take place. A significant proportion of primary infections will therefore take place before the optimal vaccination age in CRS (a) and be relatively low-risk. Since these are risk-free and do not need to be targeted in CRS (b) the age is hardly affected by the assumption of risk-free primary infections. In CRS (c) the optimal vaccination ages are much lower since successful vaccination against any two serotypes is sufficient to prevent risky infections at older ages and if vaccination also minimises the number of infections in younger individuals the risk can further be reduced despite increasing the average age of infection. Again for older vaccination ages the lifetime expected risk for all serotype combinations are very similar. Compared to CRS (c) the optimal vaccination ages in CRS (d) are much higher and again highest for combinations including DENv2. In this case it is not necessary to prevent primary infections at any age and successful vaccination against any other serotype results in risk-free subsequent infections. It is therefore better to wait until after most primary infections occurred and then vaccinate before the risk increases at older ages. Considering that the average age of infection for DENv2 is highest this means that vaccination needs to take place later if DENv2 is endemic than if it is not. Note that the optimal vaccination ages are lower for three than for two coexisting serotypes in all CRSs since the overall effective reproduction number will be higher and therefore the overall average age of




(a) The optimal vaccination ages for DENv12, DENv13, DENv14, DENv23, DENv24 and DENv34 are 788, 538, 539, 763, 756 and 544 months respectively.

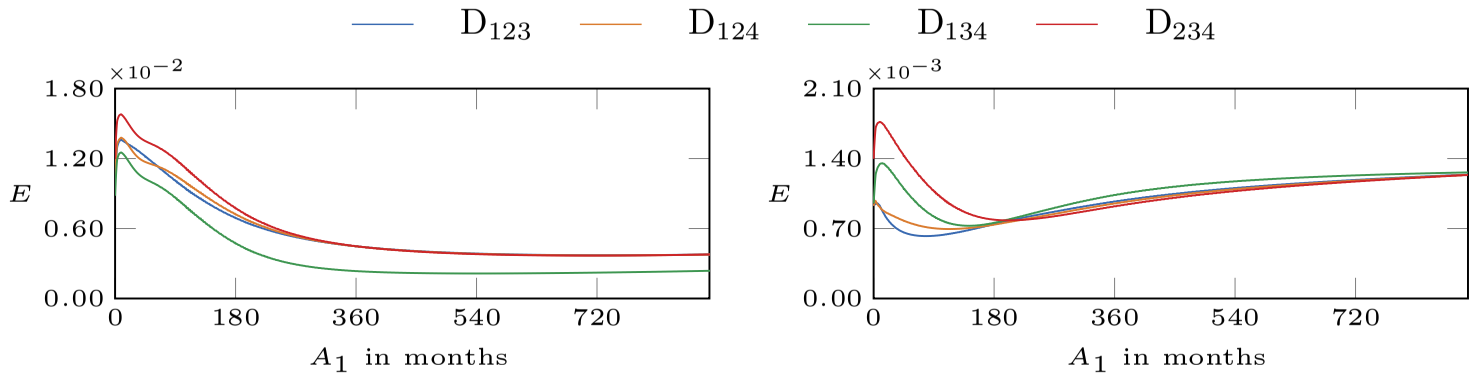
(c) The optimal vaccination ages for DENv12, DENv13, DENv14, DENv23, DENv24 and DENv34 are 104, 214, 264, 313, 348 and 328 months respectively.




(b) The optimal vaccination ages for DENv12, DENv13, DENv14, DENv23, DENv24 and DENv34 are 817, 589, 589, 794, 787 and 589 months respectively.

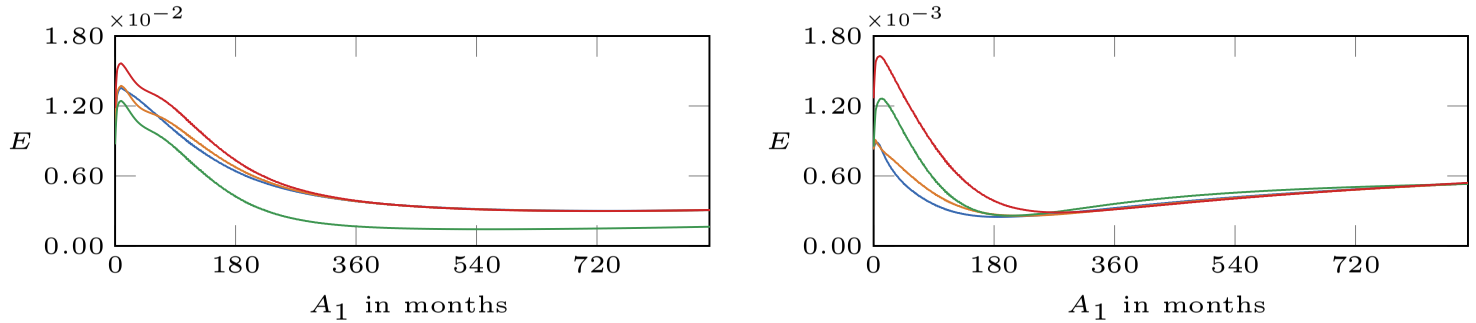
(d) The optimal vaccination ages for DENv12, DENv13, DENv14, DENv23, DENv24 and DENv34 are 368, 312, 342, 429, 458 and 412 months respectively.

Figure 4.7: The lifetime expected risk $E$ of lethality in an endemic area where two serotypes coexist as a function of age $A_1$ at which the first vaccine dose is administered. The vaccine efficacy is assumed serotype-specific but age-independent as given in Table 1.1. The subfigures (a)–(d) correspond to the CRS (a)–(d) respectively.




(a) The optimal vaccination ages for DENv123, DENv124, DENv134 and DENv234 are 734, 726, 542 and 712 months respectively.

(c) The optimal vaccination ages for DENv123, DENv124, DENv134 and DENv234 are 79, 115, 144 and 202 months respectively.




(b) The optimal vaccination ages for DENv123, DENv124, DENv134 and DENv234 are 741, 734, 557 and 719 months respectively.

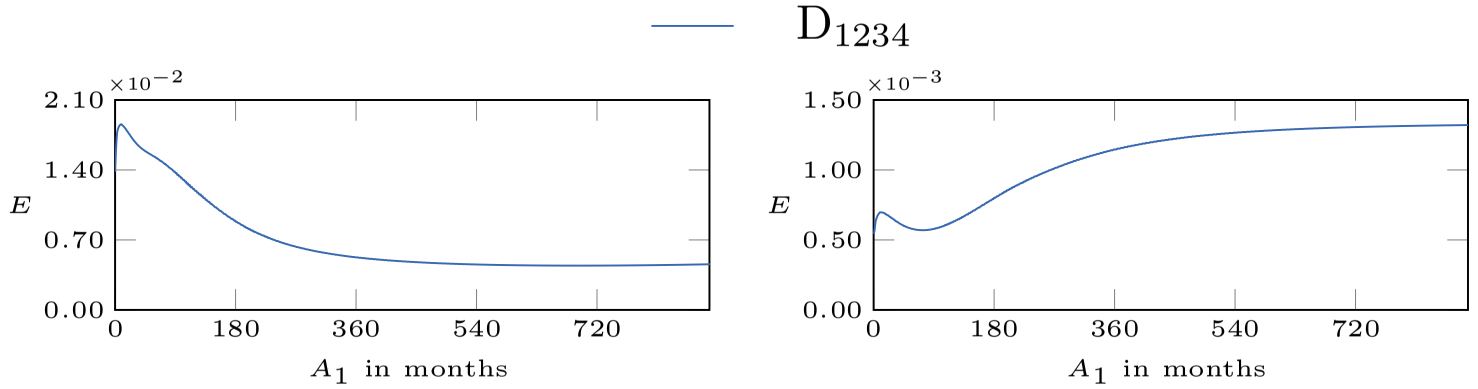
(d) The optimal vaccination ages for DENv123, DENv124, DENv134 and DENv234ß is 185, 221, 204 and 278 months respectively.

Figure 4.8: The lifetime expected risk $E$ of lethality in an endemic area where three serotypes coexist as a function of age $A_1$ at which the first vaccine dose is administered. The vaccine efficacy is assumed serotype-specific but age-independent as given in Table 1.1. The subfigures (a)–(d) correspond to the CRS (a)–(d) respectively.

infection lower so that vaccination needs to take place earlier.

Figure 4.9 shows the results for all four serotypes being endemic. In CRS (a), CRS (b) and CRS (d) the observations are very similar to two and three coexisting serotypes. However, in CRS (c) it is ideal to vaccinate at birth rather than at higher ages. Since all individuals are assumed to be completely protected by maternal antibodies at birth this is effectively a two dose vaccination strategy at 6 and 12 months which will not affect a large proportion of the population. The average age of infection in this case is not increased significantly since many vaccinated individuals will still be protected by maternal antibodies and vaccination will therefore often be unsuccessful. However, if vaccination is successful against at least two serotypes there is no subsequent risk which is why a similarly low lifetime expected risk can in fact be achieved if vaccination takes place at roughly 6.5 years. In this case vaccination is more likely to be successful against at least two serotypes so that an increase in average age of infection does not significantly increase the lifetime expected risk.

A summary of all results for a constant vaccine efficacy when the risk of lethality is minimised is given in Table 4.5. Vaccination to reduce the risk of lethality needs to take place much later in life than for hospitalisation. The only exception to this is when all four serotypes coexist in CRS (c) where the risk of lethality can be minimised by vaccinating at birth. The very high risk at old ages therefore has a significant impact on the optimal vaccination age. The most important factor is the effective reproduction number and the average age of infection that is closely related. This can clearly be seen in CRS (a) and CRS (b) if vaccination is recommended since all combinations including DENv2 require vaccination at higher ages than those without this serotype due to its low effective reproduction number. This is not true in CRS (c) and CRS (d) since the higher average age of infection is irrelevant if vaccination is successful against any two serotypes. From the table it can further be seen that in CRS (a) and CRS (b) every additional serotype results in an increase in the lifetime expected risk. In CRS (c) and CRS (d) this is not necessarily the case. In fact, in CRS (d) the lifetime expected risk decreases with an additional serotype in every case. In CRS (c) this is also true if a new serotype is introduced in an endemic area where at least two serotypes already coexist. This is due to the overall average age of infection decreasing and since post-secondary infections are risk-free very few risky infections occur at high-risk ages. In CRS (b) the optimal vaccination ages increase in comparison to CRS (a) and in CRS (d) the optimal vaccination ages increase in comparison to CRS (c)




(a) The optimal vaccination age for DENv1234 is 691 months.

(c) The optimal vaccination age for DENv1234 is 0 months.

(b) The optimal vaccination age for DENv1234 is 698 months.

(d) The optimal vaccination age for DENv1234 is 145 months.

Figure 4.9: The lifetime expected risk $E$ of lethality in an endemic area where all four serotypes coexist as a function of age $A_1$ at which the first vaccine dose is administered. The vaccine efficacy is assumed serotype-specific but age-independent as given in Table 1.1. The subfigures (a)–(d) correspond to the CRS (a)–(d) respectively.

Table 4.5: The optimal vaccination age $A_1$ in months which minimises the lifetime expected risk $E$ of lethality for all CRSs. The vaccine efficacy is assumed serotype-specific but age-independent as given in Table 1.1. '–' represents cases in which vaccination is not recommended, i.e. when $A_1$ was found to be above a reasonable age for humans.

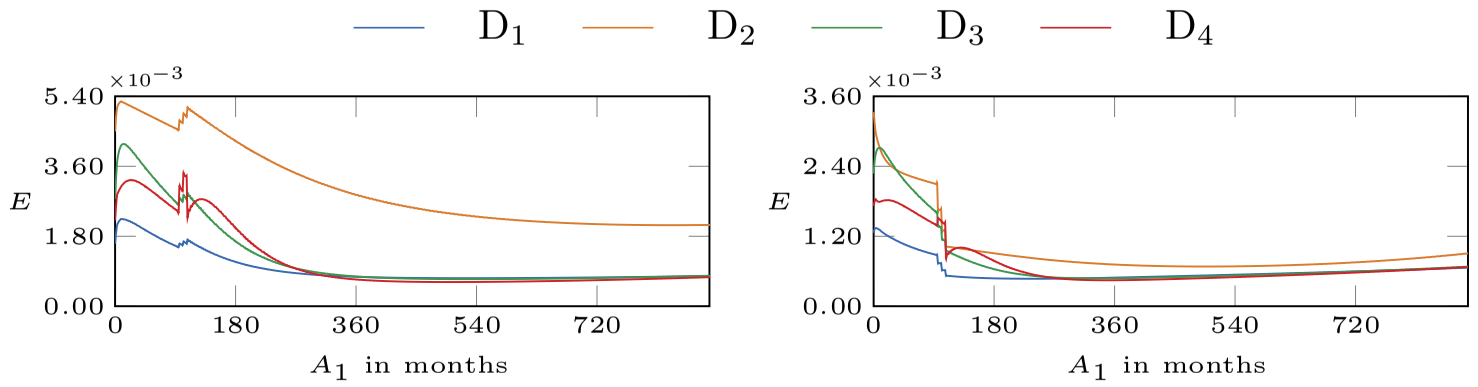
| | CRS (a) | | CRS (b) | | CRS (c) | | CRS (d) | |
|---|---|---|---|---|---|---|---|---|
| | $A_1$ | $E_{\times 10^{-4}}$ | $A_1$ | $E_{\times 10^{-4}}$ | $A_1$ | $E_{\times 10^{-4}}$ | $A_1$ | $E_{\times 10^{-4}}$ |
| DENv1 | 532 | 7.41 | – | 0.00 | 278 | 5.10 | – | 0.00 |
| DENv2 | 840 | 21.87 | – | 0.00 | 537 | 8.13 | – | 0.00 |
| DENv3 | 544 | 7.14 | – | 0.00 | 368 | 5.18 | – | 0.00 |
| DENv4 | 540 | 6.91 | – | 0.00 | 390 | 5.08 | – | 0.00 |
| DENv12 | 788 | 29.60 | 817 | 23.31 | 104 | 8.16 | 368 | 3.39 |
| DENv13 | 538 | 14.54 | 589 | 8.12 | 214 | 8.14 | 312 | 2.91 |
| DENv14 | 539 | 14.32 | 589 | 7.97 | 264 | 8.40 | 342 | 3.08 |
| DENv23 | 763 | 29.49 | 794 | 23.33 | 313 | 9.32 | 429 | 4.42 |
| DENv24 | 756 | 29.34 | 787 | 23.25 | 348 | 9.85 | 458 | 4.98 |
| DENv34 | 544 | 14.05 | 589 | 7.86 | 328 | 9.13 | 412 | 3.72 |
| DENv123 | 734 | 37.10 | 741 | 30.09 | 79 | 6.24 | 185 | 2.48 |
| DENv124 | 726 | 36.94 | 734 | 29.97 | 115 | 6.95 | 221 | 2.58 |
| DENv134 | 542 | 21.45 | 557 | 14.29 | 144 | 7.27 | 204 | 2.59 |
| DENv234 | 712 | 36.76 | 719 | 29.89 | 202 | 7.82 | 278 | 2.87 |
| DENv1234 | 691 | 44.30 | 698 | 36.78 | 0 | 5.45 | 145 | 2.27 |

since primary infections do not need to be targeted. In CRS (b) this effect is very mild since vaccination already takes place very late when many primary infections have already occurred in CRS (a). In CRS (c) it is better to vaccinate earlier even though vaccination needs to be successful against two serotypes since primary infections are risky. In CRS (d) the effect is therefore much more pronounced since primary infections are risk-free and vaccinating successfully against a single other serotype after a primary infection results in all subsequent infections being risk-free. Overall the optimal vaccination ages therefore significantly depend on the considered CRS and the effective reproduction numbers of the coexisting serotypes. The vaccine efficacy for each circulating serotype is much less relevant than in the case of hospitalisation. However, the overall efficacy is very important particularly in CRS (c) and CRS (d) since a higher efficacy against any serotype has the potential to reduce the risk caused by endemic serotypes.

### Age-Dependent Vaccine Efficacy

The age-dependent Dengvaxia efficacy is given in Table 1.1. For an endemic region with a single serotype in circulation the results with this age-dependent efficacy are presented in Figure 4.10 where the risk of lethality is minimised. Interestingly in CRS (a) and CRS (b) the increase in vaccine efficacy at 96, 102 and 108 months results in an increase in lifetime expected risk of lethality as opposed to the drops that were observed hospitalisation. The average age of infection should not be increased significantly by vaccination due to the very high risk at old ages. However, if the vaccine is more effective the average age of infection will be increased to a higher-risk age so that the higher efficacy results in a higher lifetime expected risk. In CRS (c) and CRS (d) overall the lifetime expected risk decreases with an increasing efficacy since successful vaccination against at least two serotypes results in risk-free subsequent infections. However, for DENv4 the increase in efficacy also results in a small increase in risk at 96 and 102 months but a drop at 108 months. The vaccine is less effective against all other serotypes in individuals above the age of 9 years. Consequently the probability of vaccinating successfully against two non-endemic serotypes is smaller when DENv4 is in circulation so that in this case initially an increase in risk is observed as the average age of infection rises. In CRS (c) and CRS (d) the average age of infection is less relevant since successful vaccination against any two serotypes reduces the risk. A higher efficacy against non-endemic serotypes generally decreases the risk. However, in the case of DENv4 the probability that vaccination is successful against two non-endemic serotypes is smaller than for all other serotypes so that vaccination may increase the average age of infection without infections becoming risk-free. For this serotype the increase in efficacy therefore results in a higher risk. In CRS (b) and CRS (d) vaccination is still not recommended since the lifetime expected risk is zero without it. In CRS (a) and CRS (c) the optimal vaccination ages are only slightly below those found for a constant efficacy. This is because the average age should not be drastically increased so that many infections will have already occurred and only those at very high ages are targeted. Due to the higher efficacy these high-risk infections can be targeted slightly earlier.

For several coexisting serotypes an age-dependent efficacy has very similar effects, i.e. an increase in risk in CRS (a) and CRS (b) at 96, 102 and 108 months, usually a decrease in CRS (c) and CRS (d) and little change in optimal vaccination age. In CRS (d) for DENv134 and DENv234 the lifetime expected risk increases slightly. The optimal vaccination ages together with the minimal lifetime expected risk for all scenarios are summarised in Table 4.6. In most cases an age-dependent




(a) The optimal vaccination ages for DENv1, DENv2, DENv3 and DENv4 are 525, 833, 531 and 506 months respectively.

(c) The optimal vaccination ages for DENv1, DENv2, DENv3 and DENv4 are 242, 500, 332 and 348 months respectively.

(b) Vaccination is not recommended for any serotype.

(d) Vaccination is not recommended for any serotype.

Figure 4.10: The lifetime expected risk $E$ of lethality in an endemic area where a single serotype exists as a function of age $A_1$ at which the first vaccine dose is administered. The vaccine efficacy is assumed serotype-specific and age-dependent as given in Table 1.1. The subfigures (a)–(d) correspond to the CRS (a)–(d) respectively.

Table 4.6: The optimal vaccination age $A_1$ in months which minimises the lifetime expected risk $E$ of lethality for all CRSs. The vaccine efficacy is assumed serotype-specific and age-dependent as given in Table 1.1. '–' represents cases in which vaccination is not recommended, i.e. when $A_1$ was found to be above a reasonable age for humans.

| | CRS (a) | | CRS (b) | | CRS (c) | | CRS (d) | |
|---|---|---|---|---|---|---|---|---|
| | $A_1$ | $E_{\times 10^{-4}}$ | $A_1$ | $E_{\times 10^{-4}}$ | $A_1$ | $E_{\times 10^{-4}}$ | $A_1$ | $E_{\times 10^{-4}}$ |
| DENv1 | 525 | 7.22 | – | 0.00 | 242 | 4.71 | – | 0.00 |
| DENv2 | 833 | 20.85 | – | 0.00 | 500 | 6.81 | – | 0.00 |
| DENv3 | 531 | 6.97 | – | 0.00 | 332 | 4.78 | – | 0.00 |
| DENv4 | 506 | 6.22 | – | 0.00 | 348 | 4.45 | – | 0.00 |
| DENv12 | 781 | 28.43 | 810 | 22.16 | 109 | 6.71 | 332 | 2.64 |
| DENv13 | 531 | 14.18 | 576 | 7.79 | 165 | 7.04 | 278 | 2.39 |
| DENv14 | 512 | 13.44 | 563 | 7.17 | 244 | 7.59 | 322 | 2.63 |
| DENv23 | 763 | 28.33 | 794 | 22.19 | 266 | 7.84 | 395 | 3.34 |
| DENv24 | 741 | 27.81 | 779 | 21.76 | 313 | 8.78 | 435 | 4.23 |
| DENv34 | 518 | 13.20 | 563 | 7.09 | 298 | 8.23 | 384 | 3.16 |
| DENv123 | 734 | 35.78 | 741 | 28.78 | 109 | 5.61 | 173 | 2.10 |
| DENv124 | 719 | 35.23 | 726 | 28.27 | 128 | 6.38 | 221 | 2.26 |
| DENv134 | 517 | 20.42 | 532 | 13.29 | 147 | 6.61 | 204 | 2.26 |
| DENv234 | 705 | 35.06 | 712 | 28.21 | 198 | 7.08 | 269 | 2.53 |
| DENv1234 | 684 | 42.43 | 691 | 34.92 | 7 | 5.41 | 152 | 2.01 |

efficacy leads to a slightly lower optimal vaccination age. In CRS (c) and CRS (d) this is not always the case. Some combinations of three serotypes and all four serotypes coexisting require vaccination at ages that are above those obtained for an age-independent efficacy. Sometimes this is because vaccination is ideal fairly early so that an increase in efficacy will increase the effect of vaccination and it is better to delay the vaccination until individuals reach the age of 9 years.

### Licence Restrictions

Almost all of the optimal vaccination ages that were obtained to minimise the risk of lethality are very high independent of whether a constant or an age-dependent efficacy is assumed. In fact, in CRS (a) and CRS (b) most optimal vaccination ages are above the maximum age of 45 years. In CRS (c) and CRS (d) vaccination is often ideal within the permitted age-range, however, there are some optimal vaccination ages that are below the minimum age of 9 years in CRS (c). Considering that the risk of lethality is very high at old ages and that vaccination takes place very late to prevent an increase of the average age of infection it is very important to determine the effect of the licence restriction in this case.

Table 4.7: The vaccination age $A_1$ in months which lies within the permitted age-range for the vaccine and minimises the lifetime expected risk $E$ of lethality. The percentage increase from the optimal lifetime expected risk $\delta_E\%$ is given for any case in which the optimal vaccination age lies outwith the permitted age-range of Dengvaxia. For cases in which vaccination is not recommended the minimal lifetime expected risk is zero, so that the percentage increase is given by $\infty$. The vaccine efficacy is assumed serotype-specific but age-independent as given in Table 1.1.

| | CRS (a) | | CRS (b) | | CRS (c) | | CRS (d) | |
|---|---|---|---|---|---|---|---|---|
| | $A_1$ | $\delta_E\%$ | $A_1$ | $\delta_E\%$ | $A_1$ | $\delta_E\%$ | $A_1$ | $\delta_E\%$ |
| DENv1 | 532 | – | 538 | $\infty$ | 278 | – | 539 | $\infty$ |
| DENv2 | 539 | 10 | 539 | $\infty$ | 537 | – | 539 | $\infty$ |
| DENv3 | 538 | $< 1$ | 538 | $\infty$ | 368 | – | 539 | $\infty$ |
| DENv4 | 539 | $< 1$ | 538 | $\infty$ | 390 | – | 539 | $\infty$ |
| DENv12 | 539 | 6 | 539 | 10 | 114 | $< 1$ | 368 | – |
| DENv13 | 538 | – | 538 | $< 1$ | 214 | – | 312 | – |
| DENv14 | 539 | – | 538 | $< 1$ | 264 | – | 342 | – |
| DENv23 | 539 | 6 | 539 | 9 | 313 | – | 429 | – |
| DENv24 | 539 | 5 | 539 | 9 | 348 | – | 458 | – |
| DENv34 | 538 | $< 1$ | 538 | $< 1$ | 328 | – | 412 | – |
| DENv123 | 539 | 4 | 539 | 5 | 109 | 3 | 185 | – |
| DENv124 | 539 | 4 | 539 | 5 | 115 | – | 221 | – |
| DENv134 | 538 | $< 1$ | 538 | $< 1$ | 144 | – | 204 | – |
| DENv234 | 539 | 3 | 539 | 5 | 202 | – | 278 | – |
| DENv1234 | 539 | 3 | 539 | 3 | 109 | 11 | 145 | – |

The ages at which vaccination should take place so that all doses are administered to individuals between the ages of 9 and 45 years and the percentage increase from the minimal lifetime expected risk are shown in Tables 4.7 and 4.8 for a constant and an age-dependent efficacy respectively. It is clear that similar to the risk of hospitalisation being targeted vaccination should usually take place as close to the ideal age as the restriction makes it possible, i.e. for ages below 9 years at 9 years and for ages above 45 years at 45 years. It can also be seen that the negative effect of restricting the age is very limited with no more than an 11% increase from the minimal lifetime expected risk of lethality. In comparison to the risk of hospitalisation the restriction therefore has a much smaller impact.

Table 4.8: The vaccination age $A_1$ in months which lies within the permitted age-range for the vaccine and minimises the lifetime expected risk $E$ of lethality denotes an optimal vaccination age conforming to the licence restrictions. The percentage increase from the optimal lifetime expected risk $\delta_E\%$ is given for any case in which the optimal vaccination age lies outwith the permitted age-range of Dengvaxia. For cases in which vaccination is not recommended the minimal lifetime expected risk is zero, so that the percentage increase is given by $\infty$. The vaccine efficacy is assumed serotype-specific and age-dependent as given in Table 1.1

| | CRS (a) | | CRS (b) | | CRS (c) | | CRS (d) | |
|---|---|---|---|---|---|---|---|---|
| | $A_1$ | $\delta_E\%$ | $A_1$ | $\delta_E\%$ | $A_1$ | $\delta_E\%$ | $A_1$ | $\delta_E\%$ |
| DENv1 | 525 | – | 538 | $\infty$ | 242 | – | 539 | $\infty$ |
| DENv2 | 539 | 11 | 539 | $\infty$ | 500 | – | 539 | $\infty$ |
| DENv3 | 531 | – | 538 | $\infty$ | 332 | – | 539 | $\infty$ |
| DENv4 | 506 | – | 538 | $\infty$ | 348 | – | 539 | $\infty$ |
| DENv12 | 539 | 6 | 539 | 10 | 109 | – | 332 | – |
| DENv13 | 531 | – | 538 | $< 1$ | 165 | – | 278 | – |
| DENv14 | 512 | – | 538 | $< 1$ | 244 | – | 322 | – |
| DENv23 | 539 | 6 | 539 | 10 | 266 | – | 395 | – |
| DENv24 | 539 | 5 | 539 | 10 | 313 | – | 435 | – |
| DENv34 | 518 | – | 538 | $< 1$ | 298 | – | 384 | – |
| DENv123 | 539 | 4 | 539 | 6 | 109 | – | 173 | – |
| DENv124 | 539 | 4 | 539 | 5 | 128 | – | 221 | – |
| DENv134 | 517 | – | 532 | – | 147 | – | 204 | – |
| DENv234 | 539 | 3 | 539 | 5 | 198 | – | 269 | – |
| DENv1234 | 539 | 2 | 539 | 3 | 109 | 2 | 152 | – |

### 4.4.3 Summary for Endemic Regions with Four Serotypes

In the previous two sections the simulation results for both the risk of hospitalisation and the risk of lethality were discussed based on graphs showing the lifetime expected risk plotted against the age at which vaccination is initiated. In some cases it was also pointed out that a wide range of ages led to near optimal vaccination results. Additionally the optimal vaccination age and corresponding minimal lifetime expect risk for each scenario were presented in tables. In this section the results for endemic regions in which all four serotypes coexist will be visualised in forest plots to summarise and highlight some of the key points from the previous sections in a more concise manner. The focus of this section lies on hyperendemic settings with four co-circulating serotypes since this can be considered the most likely case for most of the endemic regions of Brazil.

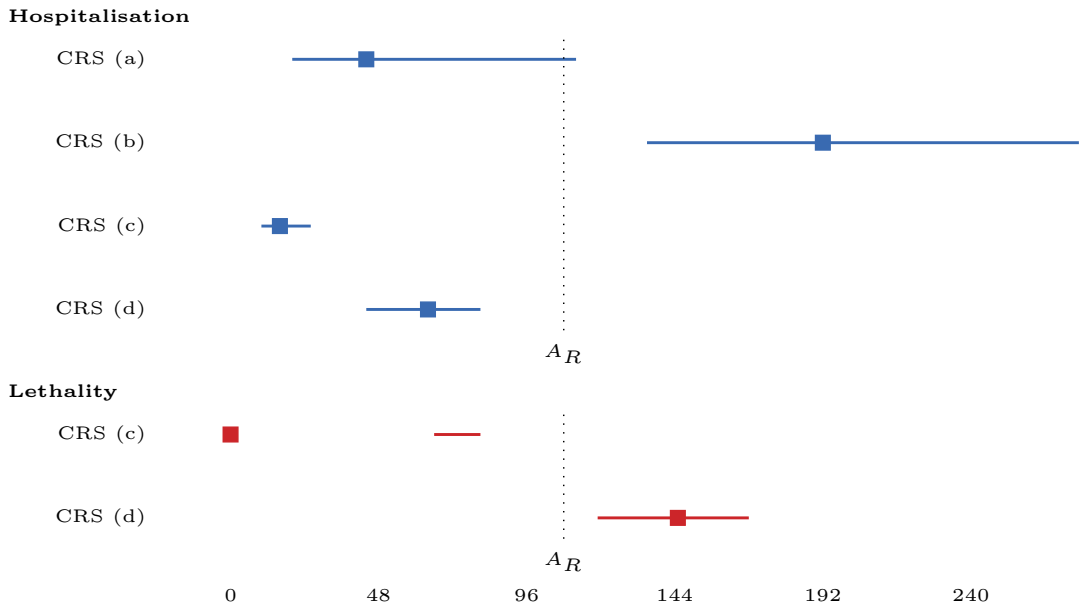



Figure 4.11: Forest plot for each scenario considering four coexisting serotypes with a constant vaccine efficacy. The squares mark the optimal vaccination age, while the horizontal lines indicate the interval in which the lifetime expected risk exceeds the minimum by no more than 5%. These intervals give an indication of the uncertainty in the optimal vaccination age. For CRS (c) when the risk of lethality is considered, two separate intervals in which the lifetime expected risk is at most 1.05 times as high as the minimum exist as shown by the discontinuous horizontal line. Note that at very young ages near-optimal vaccination is only possible at the optimal vaccination age (at birth) or at the age of one month. The vertical dotted line corresponds to the minimum age $A_R = 9$ years for vaccination according to current license restrictions. For the risk of lethality scenarios CRS (a) and CRS (b) are not shown because the optimal vaccination age and interval are much higher, i.e. the intervals start at roughly 500 months and do not end before the maximum age used for simulation.[1]

In Figures 4.11 and 4.12 forest plots for both risk functions are presented for a constant efficacy and an age-dependent efficacy respectively. The optimal vaccination ages are marked together with the range in which the lifetime expected risk differs by at most 5% from the minimum. The dotted line marks the minimal age of 9 years for which Dengvaxia is currently licensed in Brazil to make it easier to identify scenarios in which near-optimal vaccination could be carried out under

[1] In CRS (c) for the risk of lethality the lifetime expected risk is close to its minimum in two distinct age intervals. Consequently there are two distinct age ranges highlighted in the forest plot for this case. The first of these intervals is around the optimal age and very small, while the second is larger and around the age of 6 years.

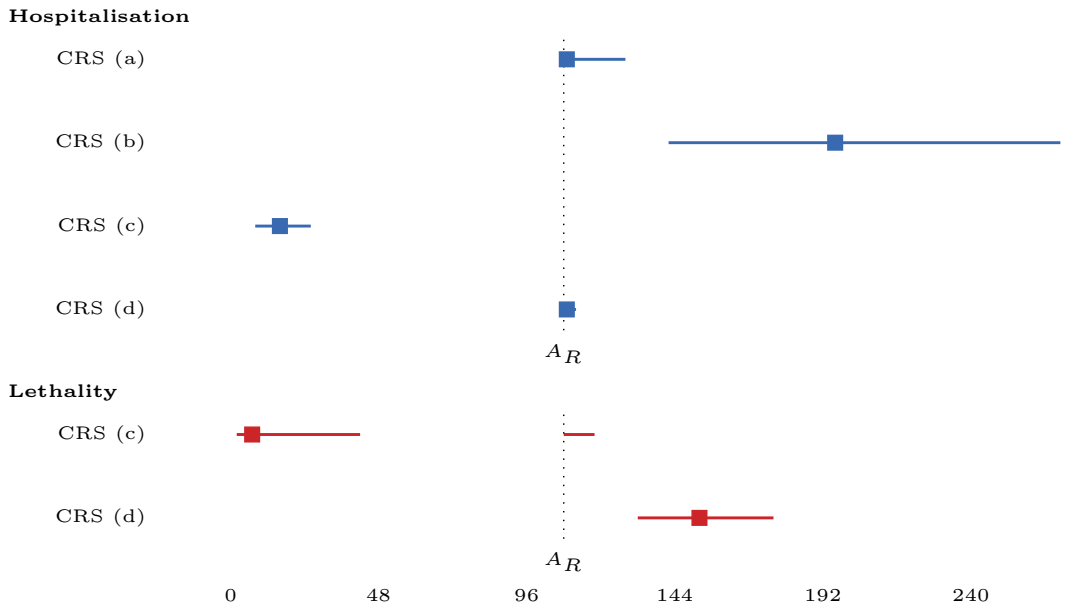



Figure 4.12: Forest plot for each scenario considering four coexisting serotypes with an age-dependent vaccine efficacy. The squares mark the optimal vaccination age, while the horizontal lines indicate the interval in which the lifetime expected risk exceeds the minimum by no more than 5%. These intervals give an indication of the uncertainty in the optimal vaccination age. For CRS (c) when the risk of lethality is considered, two separate intervals in which the lifetime expected risk is at most 1.05 times as high as the minimum exist as shown by the discontinuous horizontal line. The vertical dotted line corresponds to the minimum age $A_R = 9$ years for vaccination according to current license restrictions. For the risk of lethality scenarios CRS (a) and CRS (b) are not shown because the optimal vaccination age and interval are much higher, i.e. the intervals start at roughly 500 months and do not end before the maximum age used for simulation.[2]

the current restrictions. For the risk of hospitalisation all four CRSs are included in the plots, while for the risk of lethality only CRS (c) and CRS (d) are shown. The reason for leaving out the CRSs which do not consider PCI is that this would have led to significantly less detail in the other cases as the optimal vaccination ages were far higher than those shown in the plots and the range in which near optimal vaccination could be achieved was very large.

From Figure 4.11 it can be observed that for the risk of hospitalisation in

[2]Again in CRS (c) for the risk of lethality the lifetime expected risk is close to its minimum in two distinct age intervals. Consequently there are two distinct age ranges highlighted in the forest plot for this case with the first at very low ages and the second just after 108 months since at this age the efficacy increases abruptly. Note that this jump in efficacy is also responsible for the one sided intervals around the optimal age in CRS (a) and CRS (d) for the risk of hospitalisation.

CRS (c) and CRS (d) the range in which vaccination should take place to achieve the best results with a constant vaccine efficacy is more limited than in CRS (a) and CRS (b). Interestingly in the case of lethality in CRS (c) vaccination should be carried out at birth to achieve the minimal lifetime expected risk. However, much later in life there is a small age-range in which very good results could be achieved. Also, while CRS (a) and CRS (b) are not shown for the risk of lethality it can be deduced that the optimal vaccination age is indeed much higher than for the risk of hospitalisation. Considering near-optimal vaccination ages this is even true for CRS (c).

In the case of an age-dependent efficacy as shown in Figure 4.12 the observations for CRS (a) and CRS (b) still hold in the case of lethality. Additionally the gap in the age-range in which near-optimal results could be achieved for CRS (c) can also still be seen in this case. Indeed, for the risk of lethality very little change can be observed for any CRS other than CRS (c). However, the large effect of the age-dependent efficacy for the risk of hospitalisation becomes very apparent by comparing the two forest plots. Due to the increase in efficacy at 9 years, i.e. 108 months, all CRSs have an optimal vaccination age and near-optimal range above the minimum age for Dengvaxia with the exception of CRS (c). In CRS (c) it is least effective to delay vaccinating individuals since primary infections are risky, but post-secondary infections do not need to be targeted.

Note that the graphs also highlight the uncertainty of the optimal vaccination ages due to the sometimes very large ranges in which near optimal results could be achieved. This is an important point especially in light of the limited reliability of the data that was used to obtain these results.

## 4.5 Conclusions

In this chapter a simplified version of a dengue transmission model, which was derived and analysed in Chapter 3, was used to find the optimal vaccination age for dengue in Brazil. In particular the model was used with a constant human death rate and a constant rate at which humans get bitten by mosquitoes.

While the model describes the transmission dynamics of a single serotype only, the use of the lifetime expected risk makes it possible to include cross-reactions between the different serotypes. In particular CRSs based on ADE (risk-free primary infections) and PCI (asymptomatic post-secondary infections) were considered. The assumption of risk-free primary infections is based on the commonly accepted theory that secondary infections are more risky than primary

ones [73, 87]. Another common theory is that after two heterologous infections subsequent infections do not generally cause serious symptoms [53, 54, 115] so that relating to PCI after two heterologous infections third and fourth infections were considered to be asymptomatic. However, concerning ADE it is important to point out that while Burattini et al. [29] have found little difference in hospital admissions between primary and secondary infections this does not necessarily contradict secondary infections being more risky since primary infections are often asymptomatic. The CRSs therefore correspond to all infections being risky, primary infections being risk-free, post-secondary infections being risk-free and only secondary infections being risky respectively.

The differences between the serotypes were taken account of by using serotype-specific parameters and functions for the vaccine efficacy $\epsilon$, the effective reproduction number $R_e$ and the rate of decay of maternal antibodies $C(a)$. The vaccine efficacy was first assumed constant over all age-groups and then dependent on whether a dose was administered to individuals aged younger than 9 years or not. The effective reproduction number for each of the serotypes was determined from case report data collected through SINAN between 2000 and 2014. This required determination of the serotype-specific force of infection according to Equation (4.3) for a specific vaccination strategy. Vaccination in the routine vaccination calendar without any catch-up campaigns was aimed at minimising the lifetime expected risk due to dengue. We also considered the vaccination ages for which Dengvaxia is licensed. Once the force of infection for each serotype is known the lifetime expected risk can be determined. This was done for both the risk of hospitalisation and the risk of lethality as derived from pre-vaccine data in the previous chapter.

The different CRSs lead to different risks being associated with primary, secondary, tertiary and quaternary infections. Vaccination was assumed to correspond to a silent natural infection, so that the risk of an infection was the same for an individual with one prior natural infection as for an individual who was successfully vaccinated against one serotype before being infected. The optimal vaccination ages were determined for endemic areas with any possible combination of serotypes.

The results when the aim of vaccinating is to minimise the risk of hospitalisation are summarised in Tables 4.2 and 4.3 for a constant and age-dependent vaccine efficacy respectively and similarly in Tables 4.5 and 4.6 for lethality. The two studied risk functions are highly correlated since we expect that the more dengue cases are treated in hospital, the more deaths will be caused. However,

for the risk of lethality the risk at older ages by far surpasses the risk for children, which is not the case for hospitalisation. The high risk at older ages for lethality resulted in much higher optimal vaccination ages than for hospitalisation in almost all cases independent of whether efficacy was assumed constant or age-dependent and which CRS was considered. The reason for this is that in the case of lethality an increase of the average age of infection will lead to more high risk cases. It is therefore better not to shift this age too much. This is most easily done by vaccinating after most infections have occurred but before those at very high risk ages take place. For hospitalisation on the other hand increasing the average age of infection results in an overall lower risk and therefore it is best to vaccinate earlier.

For a single serotype in circulation it is not recommended to vaccinate if primary infections are risk-free, i.e. in CRS (b) and CRS (d). However, vaccination might be administered in order to prevent the invasion of another serotype. In this case the risk of invasion needs to be balanced out with the risk caused by the existing serotype. If vaccination takes place early an invasion might be successfully prevented, but from the graphs corresponding to CRS (b) and CRS (d) with a single serotype in circulation (cf. Figures 4.1, 4.5, 4.6 and 4.10) it can be seen that an early vaccination age leads to a high lifetime expected risk. This is due to the fact that the vaccine may not be successful against the existing serotype but against other serotypes and therefore an infection after successful vaccination can be a secondary, tertiary or quaternary infection. The natural infection will therefore be risky and would not have been without vaccination. A late vaccination age carries less risk of an infection with the existing serotype being a risky infection, but the vaccine will be less likely to prevent another serotype invading.

For the risk of hospitalisation and a constant vaccine efficacy all vaccination ages in CRS (a) and CRS (c) were found to be far below 9 years. The only exception was DENv2 existing on its own in CRS (a). In this case the risk can be minimised by vaccinating at the age of 311 months. In CRS (d) some combinations of three and four serotypes also resulted in optimal vaccination ages below the minimal age Dengvaxia is licensed for. For an age-dependent efficacy, however, only combinations of three and four coexisting serotypes in CRS (c) including DENv1 resulted in optimal ages below the minimum. On the other hand, when the risk was assumed to be lethality and the efficacy constant most serotype combinations in CRS (c) and CRS (d) resulted in vaccination ages adhering to the current licence restriction. However in CRS (a) and CRS (b) many of the optimal vaccination ages were found to be above 45 years. This was also the case for an age-dependent

efficacy. In fact the assumption of an age-dependent efficacy had much less effect on the optimal vaccination age in the case of lethality than in that of hospitalisation. However, in the case of hospitalisation the increase in efficacy resulted in a drop in lifetime expected risk while the overall behaviour of the lifetime expected risk as a function of vaccination age remained mostly unchanged. An exception to this was found to be DENv2 existing on its own in CRS (b). In this case jumps instead of drops in the lifetime expected risk could be observed due to the higher probability of DENv2 being a post-vaccine infection if the efficacy for the other serotypes increases. For the risk of lethality the behaviour was very different with an increase in lifetime expected risk in CRS (a) and CRS (b). For DENv4 the risk initially rises but then falls. The increase in risk as the higher efficacy of the older age group becomes relevant is due to the average age of infection rising more if the efficacy is higher which is not desirable if the risk of lethality is being minimised. In CRS (c) and CRS (d) most serotype combinations showed drops in the lifetime expected risk at 96, 102 and 108 months similarly to the case of hospitalisation since the increase in average age of infection is not as relevant if most infections are risk-free post-secondary infections. However, in CRS (d) the serotype combinations DENv134 and DENv234 show increases as well due to the presence of DENv4.

In Brazil Dengvaxia can only be used in individuals between the ages of 9 and 45 years. With many of the determined optimal vaccination ages below the minimum of 9 years for the risk of hospitalisation to be reduced and above the age of 45 years when lethality is targeted it is important to further investigate the age at which the vaccine should be administered under current restrictions. In particular the age for the first dose needs to be limited to be between 108 and 539 months for all three doses to be given between 9 and 45 years. The resulting ages at which vaccination should take place together with the percentage increase of the lifetime expected risk from its minimum are summarised in Tables 4.4, 4.7 and 4.8 for the risk of hospitalisation with a constant efficacy, the risk of lethality with a constant efficacy and the risk of lethality with an age-dependent efficacy respectively. In the case of hospitalisation with an age-dependent efficacy most of the optimal vaccination ages were already within the permitted age-range. The few that were below 9 years require vaccination at 9 years and lead to a fairly low percentage increase (between 5% and 28%). For an endemic region with a single serotype it is not recommended to vaccinate in CRS (b) and CRS (d). In all other cases with an optimal vaccination age below 9 years it is best to vaccinate as soon as possible after the actual minimum is reached, i.e. at 9 years.

For hospitalisation this age-restriction leads to only a small increase in lifetime expected risk of no more than 15% in CRS (a) and CRS (b). If post-secondary infections are considered asymptomatic, i.e. in CRS (c) and CRS (d), the lifetime expected risk increases by up to 200%. For the risk of lethality most optimal ages in CRS (c) and CRS (d) are already within the permitted age-range. In CRS (a) and CRS (b) ideally vaccination takes place later in life so that under current restrictions it is best to vaccinate at 45 years. Vaccinating at this age results in a percentage increase of the lifetime expected risk of no more than 11% which is comparable to the increase for hospitalisation in these CRSs but significantly less than in CRS (c) in the case of hospitalisation. The assumption regarding the age-dependence of the efficacy has very little effect on this increase when lethality is being considered.

The risk functions of hospitalisation and lethality were used as substitutes for severe dengue cases. Severe symptoms are considered more likely in secondary infections. If this is indeed the case CRS (b) and CRS (d) which consider risk-free primary infections, are more realistic. The optimal vaccination ages in these CRSs are in general much higher than the corresponding results for risky primary infections. This is to be expected since vaccination is unnecessary prior to a primary infection if this infection carries no risk for the infected individual. In fact for the risk being hospitalisation almost all optimal vaccination ages in CRS (b) and CRS (d) were found to be in the permitted age-range of 9 to 45 years independently of whether efficacy was assumed constant or age-dependent. For lethality most optimal vaccination ages in CRS (d) were found to be within the permitted age-range, but in CRS (a) and CRS (b) many of the optimal vaccination ages were found to be above 45 years. Assuming asymptomatic third and fourth infections based on few such infections being observed, i.e. CRS (c) and CRS (d), resulted in lower optimal vaccination ages than the corresponding cases in CRS (a) and CRS (b). Again this is to be expected since vaccination after a secondary infection has no effect if post-secondary infections are risk-free even without vaccination.

Overall the optimal vaccination ages varied significantly for the number of co-circulating serotypes as well as for the specific serotype combinations. The considered CRSs also played an important role. Particularly for the risk of hospitalisation the optimal vaccination ages are highly dependent on all assumptions. In CRS (a) and CRS (c) with a constant efficacy they lie between 16 and 311 months, for an age-dependent efficacy most are 109 months, however some are as low as 16 months or as high as 306 months. In CRS (b) and CRS (d) the optimal age is

between 64 and 452 months with a constant efficacy and between 109 and 440 months with an age-dependent efficacy. On the other hand for lethality and a constant efficacy the optimal vaccination ages are between 532 and 840 months in CRS (a) and CRS (b), between 0 and 537 months in CRS (c) and between 145 and 458 months in CRS (d). For an age-dependent efficacy the optimal vaccination ages are very similar if lethality is being minimised.

As pointed out before, the optimal vaccination ages vary significantly. This was due to a number of different factors each of which reflects some modelling assumption. Clearly it is necessary to make some assumptions so as to be able to express the dynamics mathematically. However, the limitations of these assumptions need to be kept in mind for the interpretation of the results.

One of the main assumptions in the presented model is the age-independence of the force of infection. It is much more realistic that the transmission of dengue is somewhat influenced by age as the behaviour of adults and children is very different when it comes to spending time outside or preventing exposure to mosquitoes. However, as a first approximation a constant biting rate and thus force of infection was assumed. As a consequence the largest age-dependent impact in the modelling framework arises due to the age-dependence of the risk functions themselves. This explains the significant differences between the optimal vaccination ages for the risk of hospitalisation and lethality in some of the considered scenarios. In Section 3.3.2 the two risk functions were derived from SINAN data. However, the data that was used for this purpose has a number of limitations such as the fact that SINAN collects dengue related medical data all over Brazil. The risk functions are therefore an average over the entire country. Considering the scale and climate zones that the country covers this is somewhat problematic since the risk in any specific part of the country may be very different from the average. The average was used as an approximation due to a lack of more refined data but it should be kept in mind that for a particular endemic region it would be advisable to determine the risk and carry out the analysis rather than to take the presented optimal vaccination ages at face value.

The derivation of the effective reproduction numbers that are a key parameter of the model can similarly be criticised since again the average is chosen. It was already discussed in Section 4.3 that the climatic conditions across Brazil vary and with them the beginning of epidemics. Indeed, some epidemics may be too localised to have been recorded as a country-wide epidemic in the SINAN data and the effective reproduction numbers might have been much higher if epidemics

had been considered at a smaller scale. It needs to be kept in mind that the optimal vaccination ages considerably depend on the reproduction number. Using a country-wide average for such an important model parameter can therefore only yield an indication and the results should only be applied if the endemic region is somewhat representative of the average behaviour.

Despite the implications form the model assumptions the results presented in this chapter demonstrate that in order to chose the most effective vaccination campaign it is crucial to determine which serotypes are endemic in the targeted area as well as to carefully consider the main aim of vaccination. Particularly serotype combinations including DENv2 showed a slightly different behaviour for both risk functions which underlines just how important it is to know which serotypes are present. The vaccine efficacy was assumed to be constant or age-dependent and the optimal vaccination ages varied significantly based on this assumption. It is being argued that the higher efficacy in children above the age of 9 years most likely depends on the presence of antibodies due to prior infections and is not due to the age per se [6, 74]. This would imply that the efficacy of Dengvaxia is poor for individuals without a prior dengue infection and only slightly better for individuals who have been infected before. Consequently results using a constant, age-independent vaccine efficacy should be considered more realistic if this is true. In any case the vaccination ages that were obtained give an indication only as to when the vaccine should be administered. This is due to simplifications such as modelling the transmission dynamics independently for the four serotypes, assuming a constant biting rate which results in an age-independent force of infection and the use of a constant human death rate $\mu_H$ which is a commonly used approximation in epidemiological modelling but is not necessarily suitable to reflect actual population dynamics in Brazil.

Chapter 5

# Optimal Vaccination Age with an Age-Dependent Biting Rate

## 5.1 Introduction

In the previous chapter optimal vaccination ages for different scenarios were obtained from a model using a constant biting rate and a constant human death rate. These simplifications made the model easy to analyse in the first instance. However, the population dynamics in Brazil are poorly described by a constant death rate and data shows that humans get bitten by mosquitoes at different rates depending on their age. More accurate vaccination ages can be found by using an age-dependent biting rate based on mosquito biting data and by describing the death rate of humans by a step-death function which is more realistic for Brazil. Additionally, in the previous chapter there was not assumed to be any difference between naturally acquired antibodies and vaccine-induced antibodies. However, in the long-term follow-up of the Dengvaxia trials an increased risk of requiring hospital treatment has been observed in seronegative recipients (cf. Section 1.4). It is important to consider this increased risk as it might mean that vaccination can do more harm than good. Particularly the effect on the optimal vaccination age is of interest when considering vaccine-induced risk.

In this chapter a model with a step-death function and an age-dependent biting rate will be used to determine the optimal vaccination age for dengue more precisely. The theoretical work required to determine the lifetime expected risk and thus the optimal vaccination age was, for the most part, carried out in Chapter 3. However, a brief summary of all important results will be given in the following section. Particularly expressions for the force of infection and the basic reproduction number of the model will be presented. The serotype-specific effect-

ive reproduction numbers will then be derived from the initial phase of recorded dengue outbreaks in Brazil similarly to how this was done in the previous chapter. Subsequently the lifetime expected risk will be computed based on hospitalisation and lethality when no vaccine-induced risk is considered. Additionally vaccine-induced risk will be considered for the risk of hospitalisation as this risk seems to depend on the infection and vaccination history of the recipient. In the case of lethality no increased risk has been observed so far and therefore only results considering the infection history but not the infection and vaccination history of recipients will be presented. The optimal vaccination age to minimise each of the considered risks will be determined for all four CRSs and both for a constant and an age-dependent vaccine efficacy. In the case of vaccine-induced risk the risk is assumed to be age-dependent only when the vaccine efficacy is age-dependent as well. For optimal vaccination ages found outwith the permitted age-range of 9 to 45 years the vaccination age will be constrained and the ideal vaccination age adhering to the Dengvaxia licence will be determined. Finally the results will be summarised and the effect of the different assumptions will be discussed.

## 5.2 Model Assumptions

The model given in Equations (3.3) to (3.5) uses a general age-dependent human death rate $\mu_H(a)$ and an age-dependent rate $q(a)$ at which mosquitoes bite humans. The steady-state force of infection for the human population, as well as two expressions for the basic reproduction number of the model were derived in Chapter 3. In the absence of data relating to the age-dependence of deaths in the human population it is possible to describe the rate at which humans die by a step-death function, i.e.

$$\mu_H(a) = \begin{cases} 0, & 0 \leq a < L, \\ \infty, & L \leq a < \infty, \end{cases} \tag{5.1}$$

where $L$ is the expected lifetime. This is a more accurate description of the population dynamics in Brazil than the commonly used constant death rate. The expected lifetime in Brazil can be taken from the literature as 73.8 years [153]; no additional data is required. The corresponding survival probability is given by

$$\pi_H(a) = e^{-\int_0^a \mu_H(s)\,\mathrm{d}s} = \begin{cases} 1, & 0 \leq a < L, \\ 0, & L \leq a < \infty. \end{cases} \tag{5.2}$$

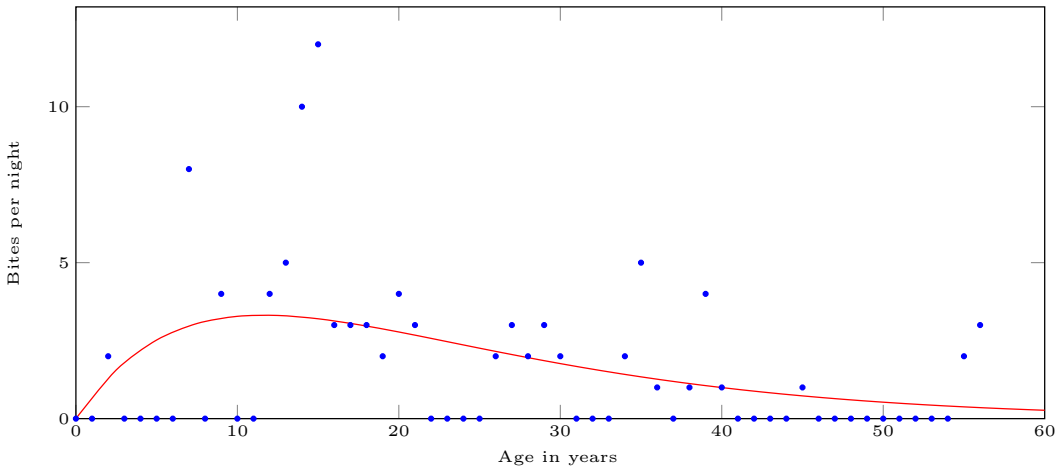



Figure 5.1: Biting rate data showing the recorded mosquito bites per night for individuals aged 0 to 56 years (blue dots) [99] and the fitted age-dependent biting rate $q(a) = k_1 a e^{-k_2 a}$ (red line).

The equilibrium age-distribution for humans with a step-death function is thus

$$N_H(a) = \frac{N_H}{L}\pi_H(a). \tag{5.3}$$

To be able to more accurately predict the optimal vaccination age for dengue the model will further be used with an age-dependent mosquito biting rate $q(a)$. Mosquito bites per night for humans of age 0 to 56 years have been recorded in Brazil as shown in Figure 5.1 and the biting rate can therefore be described by a function of the type

$$q(a) = k_1 a e^{-k_2 a} \tag{5.4}$$

where $k_1 = 282.7\,\text{year}^{-1}$ and $k_2 = 0.08593\,\text{year}^{-1}$ were obtained by fitting the function to the data (cf. Figure 5.1). The differences between how often mosquitoes bite humans of a certain age might be due to different behaviours amongst other factors, e.g. children are less aware of the danger mosquito bites pose and therefore more likely to not use prevention methods such as long sleeves or mosquito repellents.

Using an age-dependent biting rate should in theory increase the accuracy of the model. However, it is important to note that the reliability of the data is a key factor when it comes to accuracy. The data presented in Figure 5.1 clearly shows some uncertainties which can be seen as the number of reported bites is zero for a significant part of the recorded ages. This may be caused by a number

of different reasons such as that some test subjects might have been less rigorous when reporting the number of bites. Additionally a small trial cohort and thus relatively few data points for each recorded age could have caused this uncertainty. Other factors such as spatial heterogeneity might also have influenced this data set significantly, i.e. it is possible that some test subjects simply lived in areas where much fewer mosquitoes existed and thus reported fewer bites. These problems relating to the dataset are a general problem with respect to mosquito biting data and only a large study cohort could potentially lead to a higher certainty. Independent of the mode of collection and the size of the studied cohort it is also relevant to note that *Aedes aegypti* mosquitoes are known to be day-biters, i.e. they are most active just after sunrise and just before sunset and less so during the night. The data presented in Figure 5.1, however, records the number of bites per night. This data might therefore not be a particularly good representation for the main dengue vector but will be used due to the lack of a more accurate dataset. The uncertainties relating to the biting rate data must be kept in mind as they will have an effect on the optimal vaccination ages that are derived later on in this chapter.

Assuming the biting rate to be age-dependent results in the age-dependent force of infection $\lambda_H(a,t) = bq(a)I_M(t)\frac{1}{N_H}$ for the human population. At the steady-state it is given by Equation (3.15). Similarly the expressions for the reproduction number derived intuitively and via linearisation are given by Equations (3.19) and (3.22) respectively. By setting $C(a) \equiv 1$, as this is the case for almost all ages due to the rapid decline of maternal antibodies, Equations (3.19) and (3.22) yield

$$R_0 \approx \frac{mbce^{-\mu_M \tau}}{\mu_M L} \frac{k_1^2 \left[4k_2^3\omega_0 + (k_2-\gamma_H)^2\left((k_2+\gamma_H)\omega_1 + k_2\omega_2\right)\right]}{4k_2^3 (k_2+\gamma_H)^2 (k_2-\gamma_H)^2} \tag{5.5}$$

$$\text{and} \quad R_0 \approx \frac{4k_2^3\omega_0 + (k_2-\gamma_H)^2\left[(k_2+\gamma_H)\omega_1 + k_2\omega_2\right]}{\mu_M (k_2+\gamma_H)^2 (k_2-\gamma_H)^2} \frac{e^{\alpha\tau}(\mu_M+\alpha)(k_2+\gamma_H+\alpha)^2(k_2-\gamma_H-\alpha)^2}{4k_2^3\omega_3 - (k_2+\gamma_H+\alpha)^2\left[(k_2-\gamma_H-\alpha)\omega_1 + k_2\omega_2\right]} \tag{5.6}$$

respectively, where $\alpha$ is the initial exponential growth rate at the beginning of an

epidemic and

$$\begin{aligned}
\omega_0 &= \left[(k_2 L + 1)^2 - \gamma_H^2 L^2\right] e^{-2k_2 L} - \left[(k_2 + \gamma_H)\, L + 1\right] e^{-(k_2+\gamma_H)L}, \\
\omega_1 &= 1 - \left[(k_2 L + 1)\, 2k_2 L + 1\right] e^{-2k_2 L}, \\
\omega_2 &= 1 - (2k_2 L + 1)\, e^{-2k_2 L}, \text{ and} \\
\omega_3 &= 1 - \left[(k_2 + \gamma_H + \alpha)\, L + 1\right] e^{-(k_2+\gamma_H+\alpha)L}.
\end{aligned}$$

The force of infection can therefore be expressed in terms of $R_0$ by

$$\lambda(a) = \frac{\dfrac{4k_2^3 \left(k_2 + \gamma_H\right)^2 \left(k_2 - \gamma_H\right)^2}{4k_2^3 \omega_0 + \left(k_2 - \gamma_H\right)^2 \left[\left(k_2 + \gamma_H\right) \omega_1 + k_2 \omega_2\right]} q(a) R_0 \int_0^\infty q(a) i(a) \pi_H(a)\, \mathrm{d}a}{1 + \dfrac{c}{\mu_M L} \int_0^\infty q(a) i(a) \pi_H(a)\, \mathrm{d}a}. \tag{5.7}$$

The biting rate (and hence the force of infection) significantly declines for ages higher than 20 years and tends to zero for older ages. A consequence of this is that infections mainly occur in young individuals and the chance of getting infected is very low at older ages. This seems reasonable considering that dengue is commonly considered a childhood disease. However, in the next chapter it will be seen that the serological profile in Brazil indicates a residual force of infection. Such a residual force of infection means that older individuals remain at risk of infection even though the risk is much lower than that for children.

In order to determine the steady-state force of infection for each of the serotypes it is again necessary to obtain serotype-specific estimates for the effective reproduction numbers from case report data. This will be done in the next section in the same manner as for a model with a constant biting rate and a constant human death rate.

## 5.3 Effective Reproduction Numbers

All dengue outbreaks in Brazil are recorded through SINAN. Data from 2000 to 2014 showed that each serotype was responsible for several outbreaks in the covered period. This data can thus be used to find approximations for the effective reproduction number of each serotype individually very similarly to the previous chapter (cf. Section 4.3), i.e. by using Equation (5.6) with the model parameters as given in Table 3.1 and additionally $k_1 = 282.7\,\mathrm{year}^{-1}$, $k_2 = 0.08593\,\mathrm{year}^{-1}$ and $L = 73.8\,\mathrm{years}$. Again the average exponential growth rate $\alpha$ was determined from

all epidemics in the whole of Brazil and the upper and lower bounds for $\alpha$ from the mildest and strongest epidemic in any one of the five regions North, North-East, South, South-East and Centre-West. The effective reproduction numbers and upper and lower bounds are thus obtained as given in Table 5.1.

The exact values of the effective reproduction numbers are significantly influenced by the choice of the weeks that are considered to correspond to the start of an epidemic since there are climatic differences between the regions. It is therefore important to note that the effective reproduction numbers for both a constant and an age-dependent biting rate were obtained by considering the same weeks to correspond to the start of an outbreak, i.e. the same values for $\alpha$ were used in the calculations. By comparing Tables 4.1 and 5.1 it can therefore be seen that the assumption of a step-death function for humans and an age-dependent mosquito biting rate as opposed to a constant death rate and a constant biting rate have little effect on the effective reproduction numbers obtained from the initial phase of an outbreak. Note that while the two tables show no difference for the lower bounds there is in fact a difference of order $10^{-6}$ to $10^{-5}$.

Having obtained the effective reproduction number for each of the serotypes it is now possible to compute the serotype-specific forces of infection at the steady state from Equation (5.7). In particular $\lambda_i(a) = \xi_i q(a)$ was substituted and $\xi_i$ determined. The forces of infection in turn are necessary to determine the lifetime expected risk and thus the optimal vaccination age. In the next section the results obtained for the different CRSs will be presented for a number of different assumptions relating to the risk of dengue and the vaccine efficacy of Dengvaxia.

Table 5.1: Estimates of the serotype-specific effective reproduction numbers obtained from the initial exponential growth rate of epidemics when the transmission dynamics are modelled with an age-dependent biting rate and a step-death function for the human population. The data comprises all epidemics in Brazil between 2000 and 2014 for each serotype. The upper and lower bounds are taken from the highest and lowest exponential growth rates of the outbreaks in the regions North, North-East, South, South-East and Centre-West during the same period.

| Serotype | $R_e$ | lower bound | upper bound |
|---|---|---|---|
| DENv1 | 4.7045 | 1.2230 | 6.1777 |
| DENv2 | 2.9942 | 1.3745 | 8.5133 |
| DENv3 | 4.2974 | 1.4341 | 13.4129 |
| DENv4 | 4.1864 | 1.8291 | 4.8711 |

## 5.4 Optimal Vaccination Age

The lifetime expected risk for any combination of the four dengue serotypes can be computed from Equation (3.28) even though the model described in Chapter 3 is a single-serotype model. The definition of the lifetime expected risk makes this possible and can further be used to incorporate vaccine-induced risk. In particular, if it is assumed that vaccinated individuals experience the same risk as unvaccinated individuals who have antibodies to the same serotypes, the lifetime expected risk is calculated from the expected risk of an infection with serotype $i$ at age $a$ given by Equation (3.27). In this case only the infection history of an individual is relevant and successful vaccination is considered to be a silent infection. On the other hand, if the risk is assumed to depend on whether antibodies were acquired due to a natural infection or successful vaccination, the expected risk of an infection with serotype $i$ at age $a$ needs to be defined by Equation (3.26). This means that the infection and vaccination history is decisive in how risky an infection is for any individual. The reason to consider vaccine-induced risk is that an increased number of hospitalisations was observed in the long-term follow-up phase of the Dengvaxia trials particularly for seronegative vaccine recipients. This increased risk further seems to depend on the age of the recipient as shown in Table 1.2. With no such observations for the risk of lethality for the time being vaccine-induced risk can only be considered for the risk of hospitalisation. In this chapter optimal vaccination ages will therefore be determined for the risk of hospitalisation when the vaccine is assumed not to cause an increased risk, for the risk of hospitalisation with a vaccine-induced risk according to the observed number of hospitalisations in the vaccine trials and for the risk of lethality without such a vaccine-induced risk.

In the previous chapter it could already be seen that the optimal vaccination strategy aiming at minimising the risk of hospitalisation or lethality is influenced by a multitude of different factors, from the number and combination of existing serotypes, to the different CRSs and whether the vaccine efficacy is assumed constant or age-dependent. In this chapter all of these factors will therefore be considered for each of the three definitions of the lifetime expected risk (hospitalisation, hospitalisation with vaccine-induced risk and lethality). The case of hospitalisation and hospitalisation with vaccine-induced risk will be discussed in detail for a constant vaccine efficacy and briefly for an age-dependent vaccine efficacy. For the risk of lethality all results will be presented but only those for an endemic area with a single serotype in circulation will be considered to highlight any differences. Additionally the vaccination age will be restricted wherever the

optimal vaccination age lies outwith the age-range of 9 to 45 years to determine the ideal vaccination strategy under current Dengvaxia licence restrictions and determine the effect of these restrictions on the achievable lifetime expected risk.

### 5.4.1 Minimising the Risk of Hospitalisation

Let the aim of vaccination be the largest possible reduction of hospital admissions due to dengue when the vaccine does not lead to any increase in hospitalisation risk. All possible combinations of serotypes as well as the different CRSs need to be considered so as to enable policy makers to choose the best vaccination strategy for a specific endemic region. One of the many aspects of Dengvaxia that is still being challenged is the vaccine efficacy and whether it does depend on the age of the recipient or not. It is argued that the serostatus of the recipient and not the age per se determines the efficacy [4, 5]. Optimal vaccination ages will therefore be presented for a constant vaccine efficacy while the effect of an age-dependent efficacy will subsequently be discussed for an endemic area with two endemic serotypes. Both the constant and age-dependent efficacies are given in Table 1.1. Additionally the optimal strategy under current licence restrictions will be presented and the consequences of this highlighted for both efficacy assumptions.

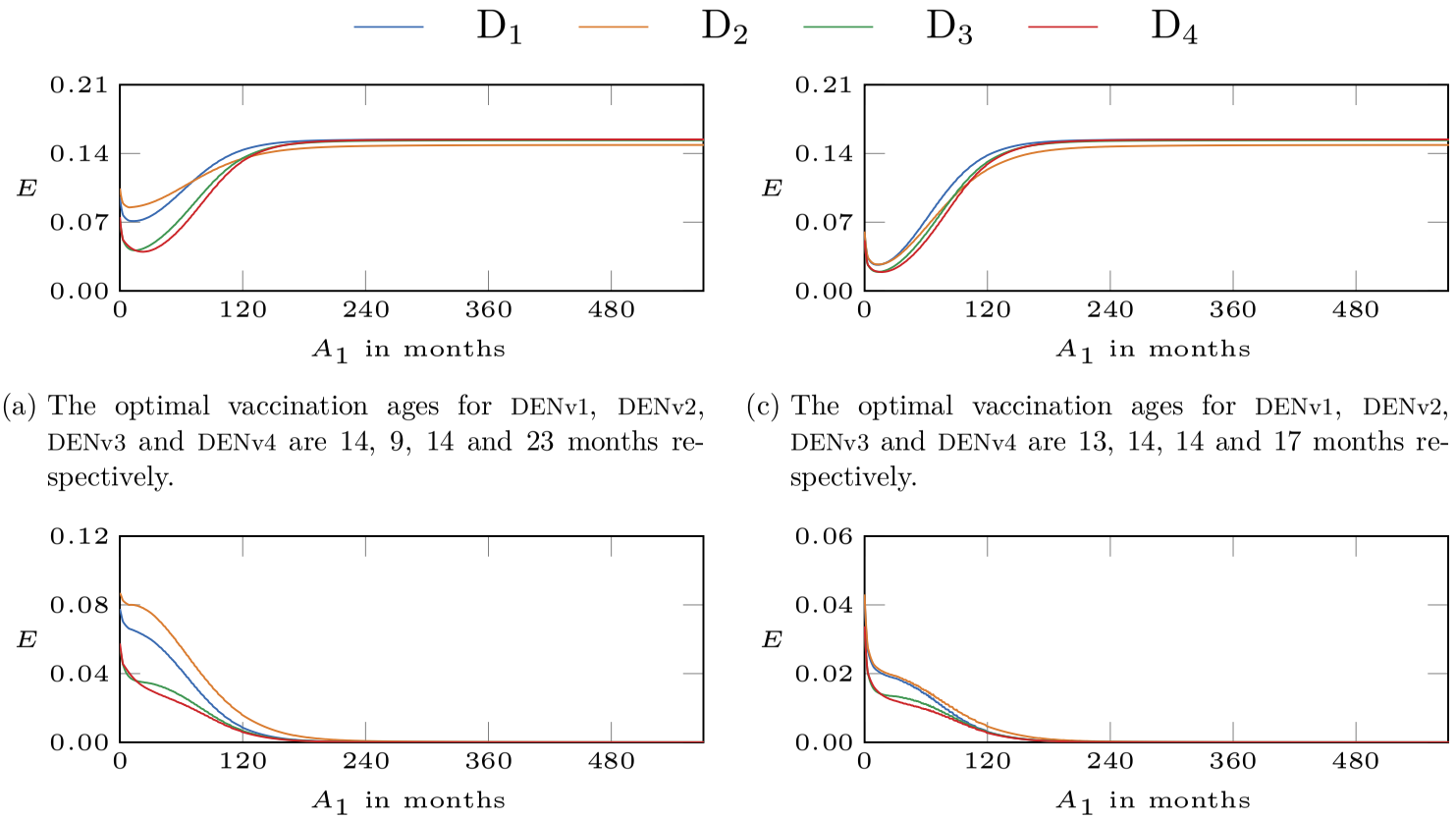
#### Constant Vaccine Efficacy

To begin with consider an endemic area with a single serotype in circulation. This is not a typical setting for dengue in Brazil where usually all four serotypes coexist. However, it can be used to understand the differences between the four serotypes more easily than in the case of several coexisting serotypes. Recall that Dengvaxia is a tetravalent but imperfect vaccine, i.e. it is not 100% effective but aims to prevent infections caused by all four dengue serotypes. In fact, the efficacy varies for the four serotypes. Due to Dengvaxia not being completely effective against all serotypes it is possible that even though only one serotype is endemic, an infection with this serotype after vaccination can be a primary, secondary, tertiary or quaternary infection. For this reason all four CRSs, CRS (a)–(d), need to be considered even if not all four serotypes coexist. In particular these CRSs correspond to combinations of risky or risk-free primary infections and symptomatic or asymptomatic post-secondary infections. For an endemic region with a single serotype the lifetime expected hospitalisation risk as a function of the age at which the first of the three vaccination doses is administered is presented in

Figure 5.2 where the subfigures (a)–(d) are numbered according to the CRSs. The optimal vaccination age is reached at the minimal lifetime expected risk.

The most striking observation from Figure 5.2 is that the lifetime expected risk can hardly be reduced if vaccination is only administered once individuals are older than approximately 20 years and cannot be improved at all for vaccination above 30 years of age. This is independent of the considered CRS and is due to the mosquito biting rate which determines the age-dependence of the force of infection. Infections mainly occur in young individuals as mentioned earlier since the biting rate tends to zero for ages above 30 years (cf. Figure 5.1). Consequently vaccination can only prevent infections if it is administered to individuals who may still get infected. This is much less likely for those older than roughly 30 years so vaccination above this age has very little effect on the lifetime expected risk.

In CRS (a) all infections have some risk associated with them. From Figure 5.2a it can be seen that in this case the optimal vaccination age for all four serotypes is very low, between 9 and 23 months. While the optimal vaccination ages are fairly similar the risk due to the different serotype varies. DENv1 and DENv2 in particular lead to a higher lifetime expected risk at young ages, i.e. a higher optimal lifetime expected risk, than DENv3 and DENv4. At older vaccination ages the risk is almost the same for all serotypes with that caused by DENv2 slightly below that of the remaining three serotypes. The reason for this is that at young ages a higher vaccine efficacy results in more prevented infections and therefore in more prevented hospitalisations, i.e. the higher the efficacy the lower the risk. This can be seen from DENv1, DENv3 and DENv4 in particular since the effective reproduction numbers for these three serotypes are rather similar but the efficacy varies from just under 55% for DENv1 to just over 70% for DENv3 and up to 77% for DENv4. However, it is important to vaccinate only once maternal antibodies have declined enough to make successful vaccination possible. Maternal antibodies decline faster for DENv3 than for DENv4 [119] so that at very young vaccination ages the risk due to DENv3 is lower even though the efficacy is not quite as high as for DENv4. At older ages only a few or even no infections can be prevented independent of the vaccine efficacy due to the age-dependence of the force of infection. Maternal antibodies have completely declined and do not play any role at older ages. The decisive factor is therefore the effective reproduction number: the lower the effective reproduction number the lower the risk. The effective reproduction number is lowest for DENv2 and thus the lifetime expected risk is lowest for this serotype. The effective reproduction numbers of the




(a) The optimal vaccination ages for DENv1, DENv2, DENv3 and DENv4 are 14, 9, 14 and 23 months respectively.

(c) The optimal vaccination ages for DENv1, DENv2, DENv3 and DENv4 are 13, 14, 14 and 17 months respectively.

(b) Vaccination is not recommended for any serotype.

(d) Vaccination is not recommended for any serotype.

Figure 5.2: The lifetime expected risk $E$ of hospitalisation in an endemic area where a single serotype exists as a function of age $A_1$ at which the first vaccine dose is administered. The vaccine efficacy is assumed serotype-specific but age-independent as given in Table 1.1. The subfigures (a)–(d) correspond to the CRS (a)–(d) respectively.

remaining serotypes vary only slightly and thus the risk due to those serotypes is almost the same if vaccination takes place at older ages.

If primary infections are risk-free but tertiary and quaternary infections symptomatic as shown in Figure 5.2b, i.e. in CRS (b), vaccination is not recommended at all. The lifetime expected risk is zero if only a single serotype is endemic but primary infections are risk-free and thus vaccination cannot reduce the risk. In contrast, vaccination will only increase the risk. This has the exact same reasons as in the case of a constant biting rate and a constant human death rate, i.e. the tetravalence of the vaccine and the fact that the vaccine is imperfect. Successful vaccination against any serotype other than the endemic serotype causes an infection to be a risky, post-primary type infection when without vaccination it would have been a risk-free, primary infection. Even though the effective reproduction number of DENv2 is low in comparison to the other serotypes the risk is most negatively affected for this serotype. The low efficacy for DENv2 means that it is more likely that individuals are successfully vaccinated against other serotypes and not immunised against DENv2. A subsequent natural infection is therefore more likely in an endemic region with only DENv2 than any other serotype and thus the lifetime expected risk is highest if vaccination takes place and only DENv2 is endemic. From Figure 5.2b it can also clearly be seen that vaccination above a certain age has almost no negative effect (even for DENv2) as the lifetime expected risk is almost zero. This is again due to the age-dependence of the force of infection since only very few natural infections are expected to occur after vaccination.

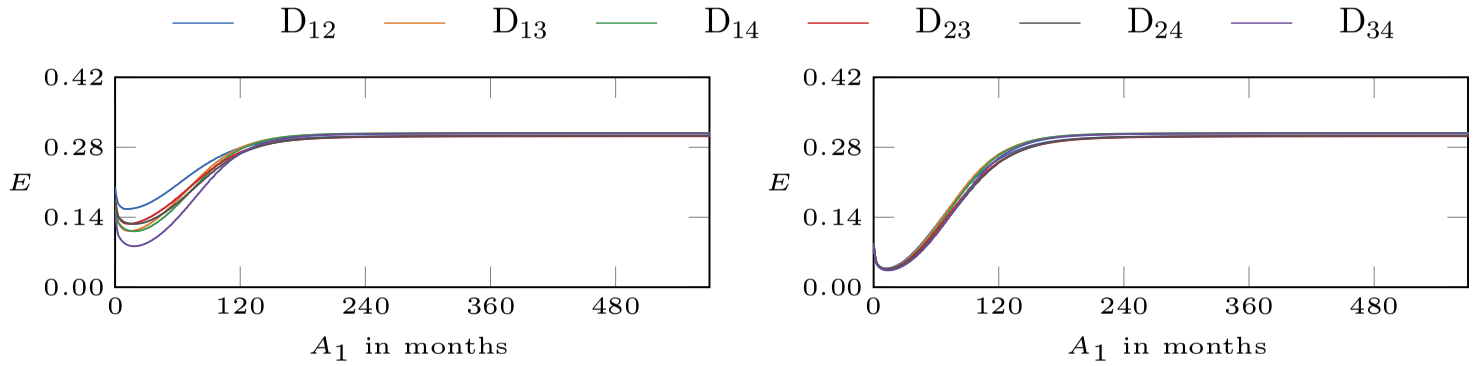
CRS (c) is presented in Figure 5.2c. In this case only primary and secondary infections have an associated risk, tertiary and quaternary infections are asymptomatic and therefore risk-free. The effect of this is noticeable in comparison to CRS (a) both through the optimal vaccination age and the lifetime expected risk for the different serotypes. The optimal vaccination ages are still very low but vary even less; they are between 13 and 17 months. Similarly the lifetime expected risk is almost identical at all ages independent of which serotype is endemic and increases quickly after the minimum is reached. This is due to the fact that vaccination after a secondary infection will no longer have any effect. The optimal vaccination age will now depend not only on the endemic serotype but on other serotypes as well since successful vaccination against at least two serotypes is sufficient to prevent all risky infections after vaccination. The vaccine efficacy is particularly high for DENv3 and DENv4 so that if vaccination against these two serotypes can be carried out successfully there will not be any post-vaccination

infection in regions where DENv3 or DENv4 is endemic and in regions where DENv1 or DENv2 is endemic an infection after vaccination will be at least a tertiary infection and therefore risk-free. In comparison to CRS (a) the lifetime expected risk is lower for any of the serotypes as would be expected since not every type of infection is risky. The effect is most pronounced for DENv1 and DENv2 since in the case of risk-free secondary infections the low efficacy against these serotypes is not as relevant due to the high efficacy against DENv3 and DENv4.

The last CRS considers only secondary infections to be risky. This scenario is presented in Figure 5.2d. It can immediately be seen that vaccination is again not recommended. After considering CRS (b) this was to be expected since without vaccination there is no risk when only a single serotype is endemic and primary infections are risk-free. The fact that tertiary and quaternary infections are assumed risk-free as well in CRS (d) leads to a lower lifetime expected risk in the case of vaccination than in CRS (b) since only secondary infections are risky as opposed to all post-primary infections, i.e. if vaccination is successful against two serotypes the individual is again at no risk in CRS (d).

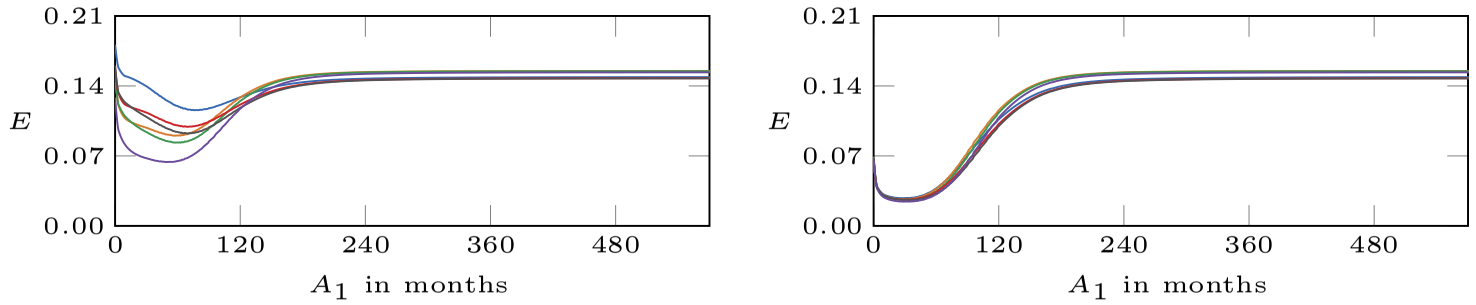
In the previous chapter an endemic area with a single serotype showed that the lifetime expected risk and optimal vaccination age significantly depends not only on the different CRSs but also on the efficacy, effective reproduction number and decay of maternal antibodies. In the case of an age-dependent biting rate the CRSs still influence the optimal age to vaccinate in an area with only one endemic serotype. In fact so does the efficacy, effective reproduction number and decay of maternal antibodies for the different serotypes. However, it is now less relevant than before which serotype is endemic. Particularly in CRS (c) there is hardly any difference in optimal vaccination age and lifetime expected risk since the combination of the different efficacies outweigh the individual efficacy. For risk-free primary infections, i.e. in CRS (b) and CRS (d) vaccination is again not recommended. Considering a single serotype has also clearly shown that the age-dependence of the biting rate and thus the force of infection significantly affects the lifetime expected risk and that vaccination cannot accomplish a significant reduction of the risk of hospitalisation at older ages in this case.

The lifetime expected risk in an endemic region with two co-existing serotypes is presented in Figure 5.3 for any serotype combination and all CRSs. Again the lifetime expected risk cannot be reduced if vaccination is administered to individuals above 30 years independent of the considered CRS. This is due to the age-dependence of the biting rate and force of infection as was the case for a single serotype in circulation. Additionally in comparison to one serotype and




(a) The optimal vaccination ages for DENv12, DENv13, DENv14, DENv23, DENv24 and DENv34 are 11, 14, 18, 14, 17 and 17 months respectively.

(c) The optimal vaccination ages for DENv12, DENv13, DENv14, DENv23, DENv24 and DENv34 are 11, 12, 13, 12, 14 and 14 months respectively.




(b) The optimal vaccination ages for DENv12, DENv13, DENv14, DENv23, DENv24 and DENv34 are 76, 58, 63, 70, 70 and 48 months respectively.

(d) The optimal vaccination ages for DENv12, DENv13, DENv14, DENv23, DENv24 and DENv34 are 28, 28, 28, 28, 35 and 28 months respectively.

Figure 5.3: The lifetime expected risk $E$ of hospitalisation in an endemic area where two serotypes coexist as a function of age $A_1$ at which the first vaccine dose is administered. The vaccine efficacy is assumed serotype-specific but age-independent as given in Table 1.1. The subfigures (a)–(d) correspond to the CRS (a)–(d) respectively.

independent of the CRS the lifetime expected risk is higher for two serotypes as one would expect.

Figure 5.3a shows the lifetime expected risk caused by the different serotype combinations in CRS (a). All of the serotype combinations lead to the same overall behaviour, i.e. the minimal lifetime expected risk and therefore the optimal vaccination age is reached at very young ages between 11 and 18 months. The lifetime expected risk increases fairly quickly after this optimal age. Interestingly most of the serotype combinations with the exception of DENv12 and DENv34 have very similar values for all vaccination ages. DENv12 results in the highest lifetime expected risk at young ages but the same as the other combinations at older ages. Additionally it requires the earliest vaccination to minimise the risk at only 11 months. This is due to the low efficacy of DENv1 and DENv2, i.e. the combined efficacy is lower than that of any other combination so that less infections can be prevented in this setting and the risk is highest. The risk can be reduced most effectively if vaccination takes place early even if some maternal antibodies persist since vaccination at a later age will not significantly decrease the number of infections due to the low efficacy. DENv34 on the other hand has the highest combined efficacy and therefore causes the lowest lifetime expected risk at young vaccination ages when many infections can be prevented. The optimal vaccination age for DENv34 is higher at 17 months due to the slower decay of maternal antibodies of DENv4. This can in fact be observed for any serotype combination including DENv4 which require later vaccination (at 17 or 18 months) than the remaining combinations (11 or 14 months). At older vaccination ages the higher efficacy is irrelevant so that all combinations lead to a very similar risk. The combined effective reproduction numbers are fairly close and are the decisive factor at older ages due to the type of biting rate used.

CRS (b) is presented in Figure 5.3b for an endemic area with two coexisting serotypes. In the case of a single serotype the assumption of risk-free primary infections meant that vaccination could only cause harm since without vaccination the lifetime expected risk was zero. For two serotypes this is no longer the case. The lifetime expected risk without vaccination can be deduced from that at older ages and is non-zero. It can be minimised for the different combinations for vaccination ages between 48 and 76 months, i.e. much later than in CRS (a). The increased optimal vaccination ages are caused by the fact that it is not necessary to target primary infections. Instead it is ideal to vaccinate before most secondary infections occur as maternal antibodies will certainly have decayed by that time. Again the impact of the low effective reproduction number and low efficacy of

DENv2 can be seen since at young ages combinations including DENv2 have a slightly higher risk than the remaining combinations due to the low efficacy, and at older vaccination ages the risk is slightly lower due to the low effective reproduction number. DENv12 needs to be considered particularly carefully. The vaccine should ideally be administered at 76 months to reduce the risk due to these two serotypes in the considered CRS. However, the impact on the lifetime expected risk is fairly small in comparison to the achievable reductions for the other serotype combinations. More than that, if vaccination takes place too early in an area with DENv12 the risk may in fact be increased, in particular for vaccination ages below 15 months. In CRS (a) vaccination for DENv12 is optimal at only 11 months. This demonstrates the importance of determining whether primary infections are risk-free or not.

In CRS (c) when two serotypes are endemic most of the observations from an area with a single serotype in circulation can be observed as shown in Figure 5.3c. The optimal vaccination ages are between 11 and 14 months. The optimum is reached early and the lifetime expected risk increases very quickly for vaccination later on. In comparison to CRS (a) the optimal vaccination ages are slightly lower. This has the same cause as in the case of one serotype, i.e. vaccination needs to take place before a secondary infection occurred as it will not have any effect otherwise. Again it can be seen that combinations including DENv4 have a slightly higher optimal vaccination age (13 or 14 months) than those without this serotype (11 or 12 months). There is hardly any difference between the lifetime expected risk caused by any of the combinations which is again due to the fact that successful vaccination against any two serotypes is sufficient to prevent all risky infections independent of whether the serotype is endemic or not. It is therefore the high efficacy of DENv3 and DENv4 that determines the optimal vaccination age. The lifetime expected risk at high vaccination ages is identical for CRS (a) and CRS (c), i.e. without vaccination (or vaccination taking place after it has any effect) the asymptomaticity of third and fourth infections is irrelevant since only two serotypes are coexisting.

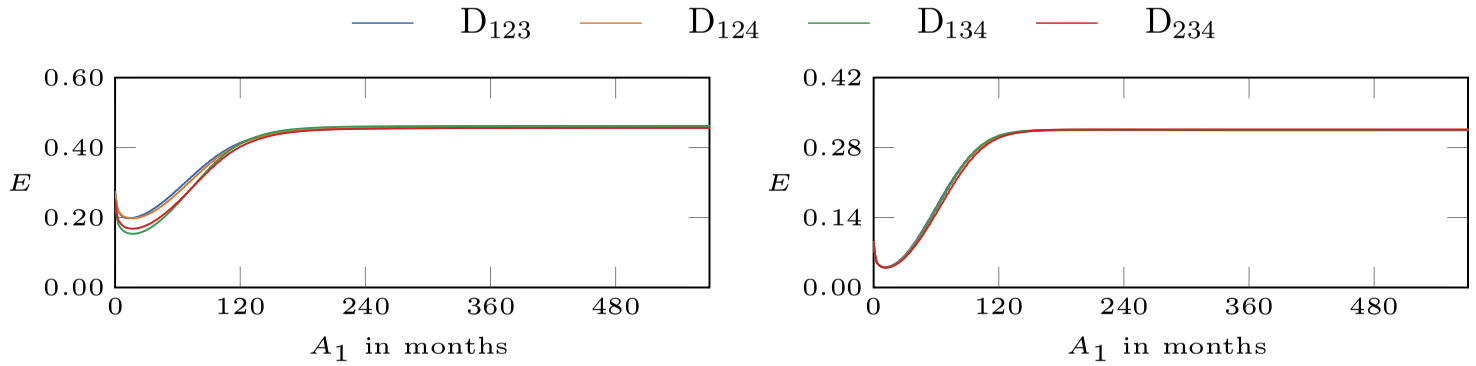
In the final CRS only secondary infections are risky. This scenario is presented in Figure 5.3d where it can be seen that the optimal vaccination age is 28 months for all combinations apart from DENv24 which requires vaccination at 35 months. However, there is a very wide range where near optimal vaccination is possible for all combinations. Primary infections do not need to be targeted as they are risk-free and vaccination after a secondary infection is futile due to the PCI caused by the secondary infection. Vaccination can therefore take place at any time up

to a secondary infection and thus there is a wider possible range of vaccination than in CRS (c). At older ages the low effective reproduction number for DENv2 again leads to a slightly lower risk for combinations with this serotype than for the other combinations. At young ages, since vaccination against two serotypes confers PCI, there is again not much difference between the risk caused by any of the combinations. If vaccination takes place too late there is no difference between the risk in CRS (b) and CRS (d).

By considering an endemic area with two circulating serotypes it can therefore be said that assuming risk-free primary infections generally leads to an increase in the optimal vaccination age, while PCI after two heterologous infections leads to a decrease. The assumption of PCI also leads to the differences between the serotypes being almost negligible.

The lifetime expected risk for all combinations of three serotypes is presented in Figure 5.4. Most of the observations for two coexisting serotypes can also be made in this case. In particular risk-free primary infections lead to an increase in optimal vaccination age due to the fact that it is better to wait until maternal antibodies have decayed before the vaccine is administered. Similarly risk-free post-secondary infections lead to a decrease in the optimal vaccination age since vaccination has to be carried out before most secondary infections occurred to have any effect at all. Again in CRS (a) and CRS (b) the serotype-specific differences in efficacy are more noticeable. DENv123 and DENv124 have a much lower combined efficacy than DENv134 and DENv234 and therefore a higher lifetime expected risk at young vaccination ages. However, in contrast to two coexisting serotypes the lifetime expected risk in CRS (c) and CRS (d) is much lower than in the corresponding CRSs with symptomatic post-secondary infection (CRS (a) and CRS (b) respectively) even if vaccination takes place at an age where it has no effect. This is to be expected since there is the possibility of a third infection even in the absence of vaccination when three serotypes are coexisting. Considering three serotypes also leads to a reduced optimal vaccination age in comparison to two coexisting serotypes as one would expect since the combined effective reproduction number increases and thus the average age of infection decreases.

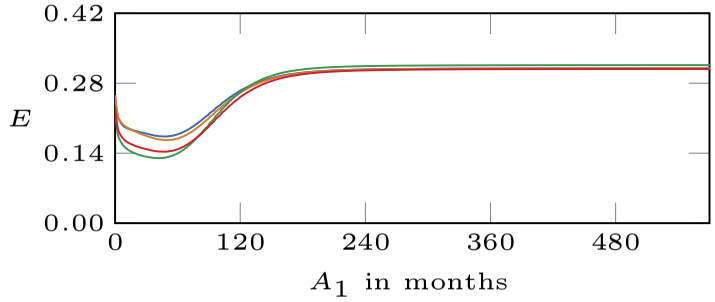
Finally the results for all four dengue serotypes coexisting in the different CRSs are presented in Figure 5.5. In most endemic regions in Brazil all four serotypes coexist. These results are therefore most interesting with respect to the optimal vaccination age. In CRS (a) the minimal lifetime expected risk can be achieved by vaccinating at 17 months; in CRS (b) the optimal age is 38 months. As before



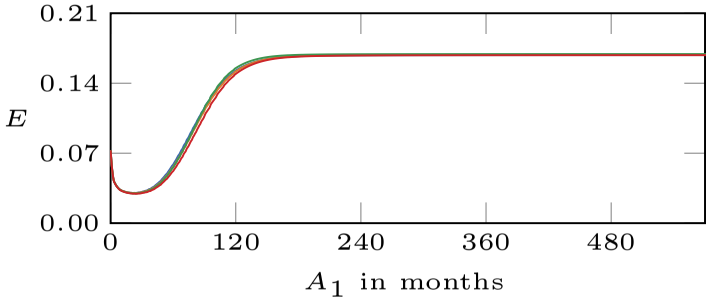

(a) The optimal vaccination ages for DENv123, DENv124, DENv134 and DENv234 are 14, 17, 17 and 17 months respectively.




(c) The optimal vaccination age is 11 months for DENv123, DENv124, DENv134 and DENv234.

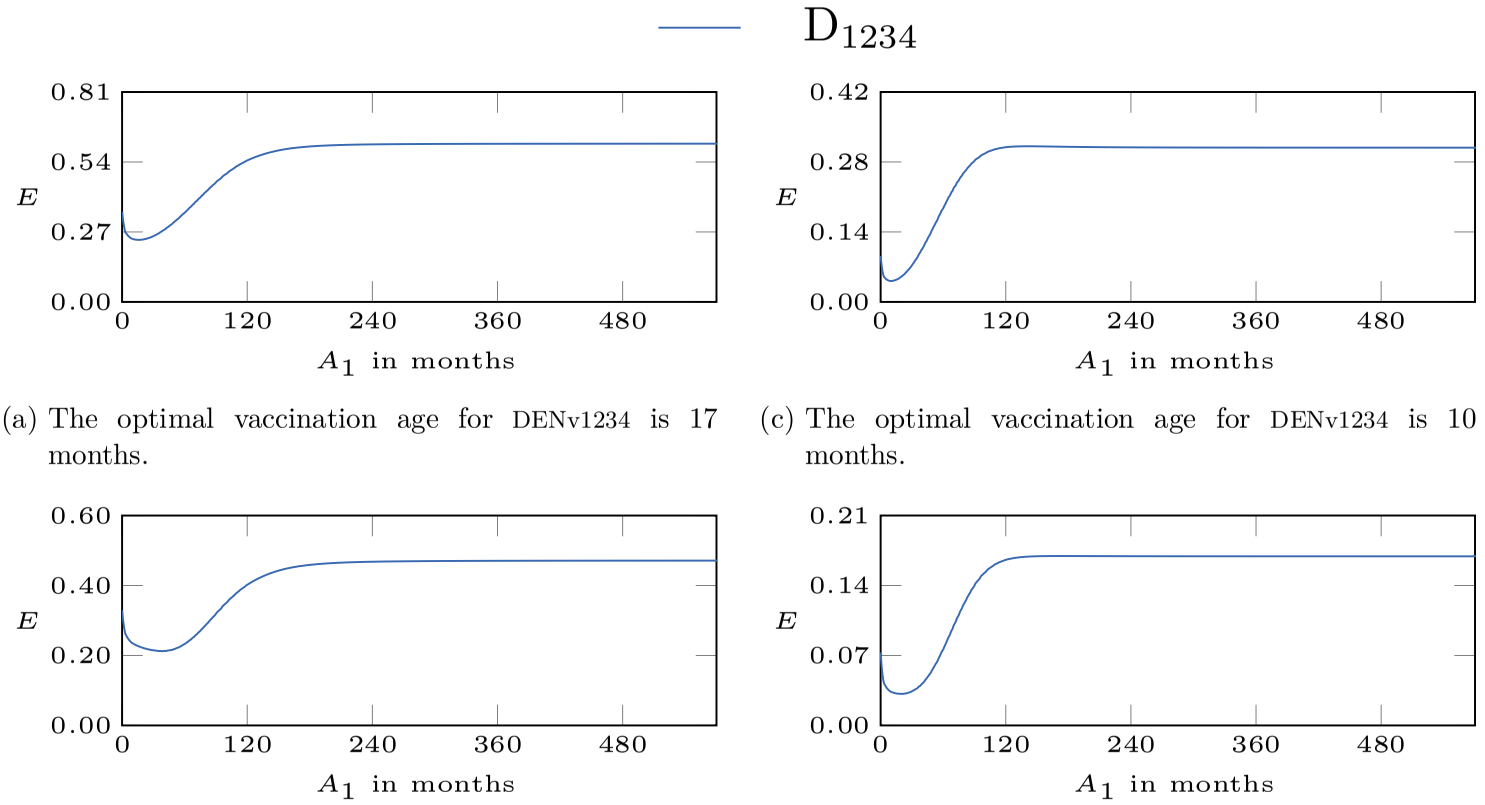



(b) The optimal vaccination ages for DENv123, DENv124, DENv134 and DENv234 are 48, 48, 42 and 48 months respectively.




(d) The optimal vaccination ages for DENv123, DENv124, DENv134 and DENv234 are 21, 24, 24 and 24 months respectively.

Figure 5.4: The lifetime expected risk $E$ of hospitalisation in an endemic area where three serotypes coexist as a function of age $A_1$ at which the first vaccine dose is administered. The vaccine efficacy is assumed serotype-specific but age-independent as given in Table 1.1. The subfigures (a)–(d) correspond to the CRS (a)–(d) respectively.




(a) The optimal vaccination age for DENv1234 is 17 months.

(c) The optimal vaccination age for DENv1234 is 10 months.

(b) The optimal vaccination age for DENv1234 is 38 months.

(d) The optimal vaccination age for DENv1234 is 21 months.

Figure 5.5: The lifetime expected risk $E$ of hospitalisation in an endemic area where all four serotypes coexist as a function of age $A_1$ at which the first vaccine dose is administered. The vaccine efficacy is assumed serotype-specific but age-independent as given in Table 1.1. The subfigures (a)–(d) correspond to the CRS (a)–(d) respectively.

the corresponding optimal vaccination age decreases if PCI is considered after two heterologous infections so that in CRS (c) the optimal vaccination age is 10 months and in CRS (d) it is 21 months. Additionally the lifetime expected risk decreases in CRS (c) and CRS (d) compared to CRS (a) and CRS (b) for any vaccination age as one would expect. The overall behaviour of the lifetime expected risk is similar to the case of two or three coexisting serotypes for any of the CRSs and will therefore not be discussed in any more detail.

The previously presented optimal vaccination ages are summarised in Table 5.2 where the corresponding minimal lifetime expected risk is given for any number and combination of dengue serotypes. From the table it becomes very clear that the optimal vaccination ages for any CRS vary little. The optimal vaccination age lies between 9 and 23 months for CRS (a), between 38 and 76 months for CRS (b), between 10 and 17 months for CRS (c) and between 21 and 35 months for CRS (d). None of the optimal vaccination ages are therefore within the permitted age-range of 9 to 45 years for Dengvaxia. For a single serotype and risk-free primary infections (CRS (b) and CRS (d)) vaccination is not recommended. In each CRS the lifetime expected risk increases if an additional serotype is in circulation, e.g. in

Table 5.2: The optimal vaccination age $A_1$ in months which minimises the lifetime expected risk $E$ of hospitalisation for all CRSs. The vaccine efficacy is assumed serotype-specific but age-independent as given in Table 1.1. '–' represents cases in which vaccination is not recommended, i.e. when $A_1$ was found to be above the expected lifetime $L$.

| | CRS (a) | | CRS (b) | | CRS (c) | | CRS (d) | |
|---|---|---|---|---|---|---|---|---|
| | $A_1$ | $E_{\times 10^{-2}}$ | $A_1$ | $E_{\times 10^{-2}}$ | $A_1$ | $E_{\times 10^{-2}}$ | $A_1$ | $E_{\times 10^{-2}}$ |
| DENv1 | 14 | 7.12 | – | 0.00 | 13 | 2.66 | – | 0.00 |
| DENv2 | 9 | 8.51 | – | 0.00 | 14 | 2.70 | – | 0.00 |
| DENv3 | 14 | 4.13 | – | 0.00 | 14 | 1.95 | – | 0.00 |
| DENv4 | 23 | 3.99 | – | 0.00 | 17 | 1.92 | – | 0.00 |
| DENv12 | 11 | 15.64 | 76 | 11.57 | 11 | 3.78 | 28 | 2.77 |
| DENv13 | 14 | 11.25 | 58 | 9.02 | 12 | 3.66 | 28 | 2.67 |
| DENv14 | 18 | 11.20 | 63 | 8.33 | 13 | 3.64 | 28 | 2.64 |
| DENv23 | 14 | 12.69 | 70 | 9.91 | 12 | 3.60 | 28 | 2.63 |
| DENv24 | 17 | 12.66 | 70 | 9.24 | 14 | 3.58 | 35 | 2.59 |
| DENv34 | 17 | 8.20 | 48 | 6.39 | 14 | 3.37 | 28 | 2.43 |
| DENv123 | 14 | 19.80 | 48 | 17.33 | 11 | 4.04 | 21 | 3.02 |
| DENv124 | 17 | 19.80 | 48 | 16.60 | 11 | 4.03 | 24 | 3.01 |
| DENv134 | 17 | 15.34 | 42 | 13.00 | 11 | 3.99 | 24 | 2.97 |
| DENv234 | 17 | 16.81 | 48 | 14.29 | 11 | 3.95 | 24 | 2.94 |
| DENv1234 | 17 | 23.94 | 38 | 21.23 | 10 | 4.19 | 21 | 3.16 |

CRS (d) if DENv3 is introduced when DENv1 and DENv2 are already endemic the lifetime expected risk increases from $2.77\times10^{-2}$ to $3.02\times10^{-2}$. In contrast to the model with a constant biting rate there are no exceptions to this. This is due to the age-dependence of the biting rate and force of infection in the model that is being considered in this chapter. All infections occur relatively early due to the biting rate function and with an increasing number of serotypes the average age of infection gets further decreased to ages at which the associated risk is even higher. This results in an increase in lifetime expected risk as the number of serotypes increases independent of the CRS. It is also noticeable that in CRS (b) and CRS (d) the increasing number of serotypes leads to a decrease in optimal vaccination age. The reason for this is similarly that the average age of infection decreases but vaccination needs to take place before most secondary infections occur. For an age-dependent biting rate and a step-death function the optimal vaccination age in the case of a constant vaccine efficacy therefore mainly depends on the CRS and very little on other factors such as the number of serotypes in circulation. The specific serotype combinations are most relevant in CRS (b).

### Age-Dependent Vaccine Efficacy

It is still being discussed whether the efficacy of Dengvaxia is age-dependent or constant. Some scientists argue that the differences that were recorded in the age-groups of the vaccine trials [32, 66] are in fact due to the serostatus of the recipient [4, 5]. Clearly the likelihood of being seropositive increases with age so that it is difficult to determine which factor is decisive and more research into this aspect of dengue vaccination is needed. For a full picture the results for an age-dependent vaccine efficacy as given in Table 1.1 are summarised in Table 5.3. In comparison to the constant efficacy case as presented in Table 5.2 it can be seen that assuming an age-dependent efficacy has very little effect on the optimal vaccination ages independent of the considered CRS. CRS (a) requires vaccination between 9 and 22 months as opposed to 9 and 23 months in the constant efficacy case. Similarly the optimal vaccination ages in CRS (c) are between 11 and 17 months instead of between 10 and 17 months. In the case of risk-free primary infections the age-dependence of the efficacy has some impact on the optimal vaccination ages. In CRS (d) the ages vary between 24 and 42 months (21 and 35 in the constant efficacy case) and in CRS (b) the optimal ages for most combinations with two serotypes are 108 months and therefore much higher than before (between 38 and 76 months). Due to the lower efficacy in the age-group below 9 years in comparison to the pooled efficacy it is not surprising that the lifetime expected

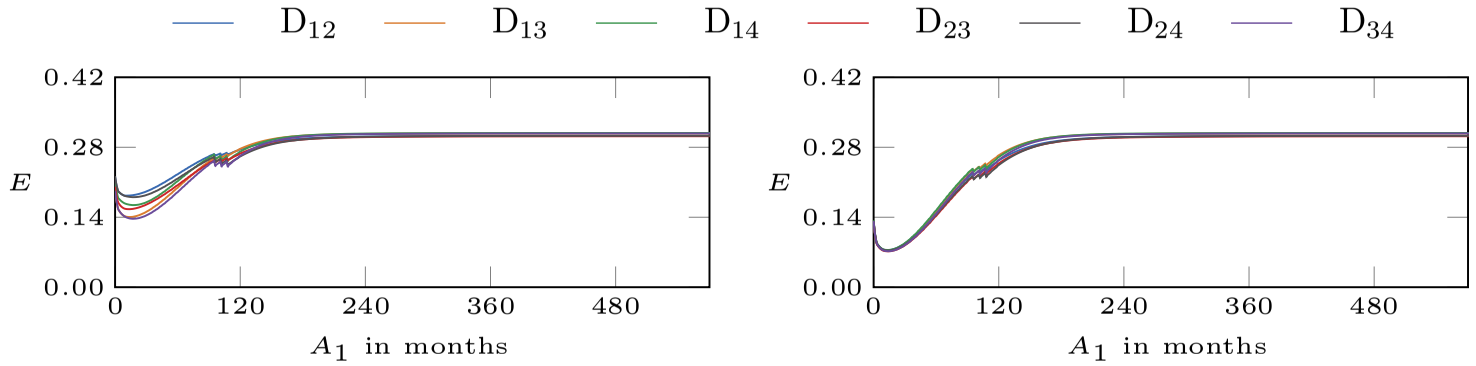
Table 5.3: The optimal vaccination age $A_1$ in months which minimises the lifetime expected risk $E$ of hospitalisation for all CRSs. The vaccine efficacy is assumed serotype-specific and age-dependent as given in Table 1.1. '–' represents cases in which vaccination is not recommended, i.e. when $A_1$ was found to be above a reasonable age for humans.

| | CRS (a) | | CRS (b) | | CRS (c) | | CRS (d) | |
|---|---|---|---|---|---|---|---|---|
| | $A_1$ | $E_{\times 10^{-2}}$ | $A_1$ | $E_{\times 10^{-2}}$ | $A_1$ | $E_{\times 10^{-2}}$ | $A_1$ | $E_{\times 10^{-2}}$ |
| DENv1 | 14 | 8.39 | – | 0.00 | 14 | 4.92 | – | 0.00 |
| DENv2 | 9 | 9.92 | – | 0.00 | 14 | 5.13 | – | 0.00 |
| DENv3 | 14 | 5.65 | – | 0.00 | 14 | 3.75 | – | 0.00 |
| DENv4 | 22 | 7.98 | – | 0.00 | 17 | 4.75 | – | 0.00 |
| DENv12 | 11 | 18.32 | 108 | 12.06 | 14 | 7.42 | 42 | 5.01 |
| DENv13 | 14 | 14.04 | 63 | 10.41 | 14 | 7.29 | 38 | 5.01 |
| DENv14 | 17 | 16.43 | 108 | 10.77 | 14 | 7.45 | 38 | 5.08 |
| DENv23 | 14 | 15.61 | 108 | 11.13 | 14 | 7.18 | 42 | 4.90 |
| DENv24 | 17 | 18.02 | 108 | 10.34 | 14 | 7.36 | 42 | 4.96 |
| DENv34 | 17 | 13.69 | 108 | 9.83 | 14 | 7.20 | 38 | 4.95 |
| DENv123 | 14 | 24.00 | 48 | 20.13 | 11 | 7.90 | 28 | 5.63 |
| DENv124 | 17 | 26.43 | 55 | 21.51 | 11 | 7.91 | 28 | 5.63 |
| DENv134 | 17 | 22.10 | 43 | 18.23 | 11 | 7.93 | 28 | 5.69 |
| DENv234 | 17 | 23.69 | 49 | 19.47 | 11 | 7.88 | 28 | 5.63 |
| DENv1234 | 16 | 32.10 | 39 | 27.96 | 11 | 8.05 | 24 | 5.83 |

risk is higher in the case of an age-dependent efficacy than for a constant efficacy. This is true even for two serotypes being endemic in CRS (b). In the case of risk-free primary infections vaccination is still not recommended if only a single serotype is in circulation due to the risk being zero without vaccination.

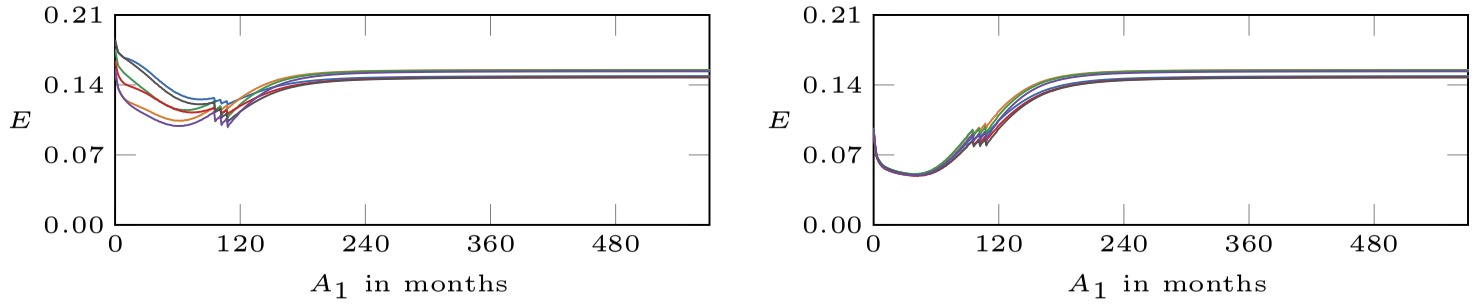
Only some results for regions with two endemic serotypes are affected by the assumption of an age-dependent efficacy while the remaining cases for any number of serotypes are unaffected. The results for two coexisting serotypes are therefore presented in Figure 5.6 to discuss the effect and why in most cases there is none.

As in the previous chapter the effect of the age-dependence on the lifetime expected risk is apparent due to the drops that occur whenever a vaccination age is reached at which an additional dose is administered with the higher efficacy in the age-group above 9 years. This is the case in all four CRSs. Due to the low average ages of infection vaccination generally should take place very early. The risk in CRS (a), CRS (c) and CRS (d) is very low at early ages and increases drastically thereafter so that even though the increase in efficacy decreases the lifetime expected risk it does not decrease it enough to reach a minimum this late. Note that the same is true for serotype combinations of one, three or four




(a) The optimal vaccination ages for DENv12, DENv13, DENv14, DENv23, DENv24 and DENv34 are 11, 14, 17, 14, 17 and 17 months respectively.

(c) The optimal vaccination age is 14 months for DENv12, DENv13, DENv14, DENv23, DENv24 and DENv34.




(b) The optimal vaccination ages for DENv12, DENv13, DENv14, DENv23, DENv24 and DENv34 are 108, 63, 108, 108, 108 and 108 months respectively.

(d) The optimal vaccination ages for DENv12, DENv13, DENv14, DENv23, DENv24 and DENv34 are 42, 38, 38, 42, 42 and 38 months respectively.

Figure 5.6: The lifetime expected risk $E$ of hospitalisation in an endemic area where two serotypes coexist as a function of age $A_1$ at which the first vaccine dose is administered. The vaccine efficacy is assumed serotype-specific and age-dependent as given in Table 1.1. The subfigures (a)–(d) correspond to the CRS (a)–(d) respectively.

serotypes in CRS (c) and of three and four serotypes in CRS (a) and CRS (d). This is not shown here explicitly but can be deduced from the corresponding graphs in the constant efficacy case, i.e. the steep increase after the minimum is reached at very young ages. The situation is slightly different in CRS (b) where most serotype combinations require vaccination at a later age and there is a much slower increase in lifetime expected risk after the optimal vaccination age. The combination of these two factors together with the significant increase in efficacy above 9 years leads to cases in which the lifetime expected risk only reaches its minimum once all three doses are given with the higher efficacy, i.e. at 108 months. By considering Figures 5.4b and 5.5b it also becomes apparent why there is no effect like this for three and four coexisting serotypes as the lifetime expected risk as a function of the age at which the first vaccination dose is administered is much steeper than for two serotypes. For a single serotype in existence the drops in lifetime expected risk are irrelevant since without vaccination the risk is certainly zero.

### Licence Restrictions

Both a constant and an age-dependent vaccine efficacy result in optimal vaccination ages outwith the age-range of 9 to 45 years for which Dengvaxia is currently licensed in Brazil. In fact only CRS (b) in the case of an age-dependent efficacy and two coexisting serotypes results in vaccination ages that adhere to this restriction while all other vaccination ages are far below 9 years. However, it is important to determine what can be achieved with the current licence. The vaccination ages are therefore restricted to be between 9 to 45 years, i.e. the first dose needs to be administered between 108 and 539 months. The vaccination ages that lead to the best results under this constraint for a constant and an age-dependent vaccine efficacy are presented in Tables 5.4 and 5.5 respectively. It can immediately be seen that it is best to carry out the vaccination campaign as close to the ideal vaccination age as possible. For low optimal ages vaccination should therefore be administered to individuals aged 108 months. For a single serotype in existence when primary infections are risk-free the least harm is done by vaccinating at 538 months which can be understood to be as late as possible.

From Table 5.4 the impact of the licence restriction becomes clear when considering the percentage increase from the minimal lifetime expected risk that is caused by having to wait with vaccination until individuals turn 9 years old. In CRS (a) this increase varies between 53% and 207%, in CRS (b) between 7% and 84%, in CRS (c) between 327% and 630% and in CRS (d) between 227% and 406%. The negative effect of the licence restriction is therefore most noticeable if

Table 5.4: The vaccination age $A_1$ in months which lies within the permitted age-range for the vaccine and minimises the lifetime expected risk $E$ of hospitalisation. The percentage increase from the optimal lifetime expected risk $\delta_E\%$ is given for any case in which the optimal vaccination age lies outwith the permitted age-range of Dengvaxia. For cases in which vaccination is not recommended the minimal lifetime expected risk is zero, so that the percentage increase is given by $\infty$. The vaccine efficacy is assumed serotype-specific but age-independent as given in Table 1.1.

| | CRS (a) | | CRS (b) | | CRS (c) | | CRS (d) | |
|---|---|---|---|---|---|---|---|---|
| | $A_1$ | $\delta_E\%$ | $A_1$ | $\delta_E\%$ | $A_1$ | $\delta_E\%$ | $A_1$ | $\delta_E\%$ |
| DENv1 | 108 | 95 | 538 | $\infty$ | 108 | 389 | 538 | $\infty$ |
| DENv2 | 108 | 53 | 538 | $\infty$ | 108 | 327 | 538 | $\infty$ |
| DENv3 | 108 | 207 | 538 | $\infty$ | 108 | 523 | 538 | $\infty$ |
| DENv4 | 108 | 206 | 538 | $\infty$ | 108 | 511 | 538 | $\infty$ |
| DENv12 | 108 | 72 | 108 | 7 | 108 | 530 | 108 | 235 |
| DENv13 | 108 | 136 | 108 | 32 | 108 | 574 | 108 | 275 |
| DENv14 | 108 | 133 | 108 | 37 | 108 | 567 | 108 | 267 |
| DENv23 | 108 | 103 | 108 | 15 | 108 | 540 | 108 | 232 |
| DENv24 | 108 | 99 | 108 | 19 | 108 | 535 | 108 | 227 |
| DENv34 | 108 | 203 | 108 | 63 | 108 | 599 | 108 | 275 |
| DENv123 | 108 | 100 | 108 | 43 | 108 | 614 | 108 | 368 |
| DENv124 | 108 | 97 | 108 | 46 | 108 | 614 | 108 | 365 |
| DENv134 | 108 | 152 | 108 | 84 | 108 | 630 | 108 | 383 |
| DENv234 | 108 | 126 | 108 | 62 | 108 | 620 | 108 | 364 |
| DENv1234 | 108 | 116 | 108 | 76 | 108 | 626 | 108 | 406 |

two heterologous infections confer PCI and lowest if all but primary infections are risky. This trend can also be observed in the case of an age-dependent efficacy (cf. Table 5.5) albeit the overall percentage increase is much lower due to the higher efficacy at 9 years for an age-dependent efficacy compared to the pooled efficacy at 9 years. In scenarios with optimal vaccination ages outwith the permitted age-range the percentage increase varies between 8% and as much as 276%. This is still small in comparison to the constant vaccine efficacy case.

The licence restriction therefore has a significant negative effect on the achievable lifetime expected risk. It would be possible to reduce the lifetime expected risk much further if vaccination below 9 years were to be permitted. This is especially true if PCI is considered. In the case of an age-dependent biting rate even the assumption of an age-dependent efficacy does not lead to an improvement of this situation, i.e. the licence restrictions make a successful vaccination campaign more difficult in either case.

Table 5.5: The vaccination age $A_1$ in months which lies within the permitted age-range for the vaccine and minimises the lifetime expected risk $E$ of hospitalisation. The percentage increase from the optimal lifetime expected risk $\delta_E\%$ is given for any case in which the optimal vaccination age lies outwith the permitted age-range of Dengvaxia. For cases in which vaccination is not recommended the minimal lifetime expected risk is zero, so that the percentage increase is given by $\infty$. The vaccine efficacy is assumed serotype-specific and age-dependent as given in Table 1.1.

| | CRS (a) | | CRS (b) | | CRS (c) | | CRS (d) | |
|---|---|---|---|---|---|---|---|---|
| | $A_1$ | $\delta_E\%$ | $A_1$ | $\delta_E\%$ | $A_1$ | $\delta_E\%$ | $A_1$ | $\delta_E\%$ |
| DENv1 | 108 | 63 | 538 | $\infty$ | 108 | 161 | 538 | $\infty$ |
| DENv2 | 108 | 29 | 538 | $\infty$ | 108 | 119 | 538 | $\infty$ |
| DENv3 | 108 | 122 | 538 | $\infty$ | 108 | 218 | 538 | $\infty$ |
| DENv4 | 108 | 46 | 538 | $\infty$ | 108 | 136 | 538 | $\infty$ |
| DENv12 | 108 | 45 | 108 | – | 108 | 216 | 108 | 80 |
| DENv13 | 108 | 87 | 108 | 12 | 108 | 233 | 108 | 94 |
| DENv14 | 108 | 54 | 108 | – | 108 | 218 | 108 | 81 |
| DENv23 | 108 | 62 | 108 | – | 108 | 215 | 108 | 72 |
| DENv24 | 108 | 36 | 108 | – | 108 | 200 | 108 | 61 |
| DENv34 | 108 | 76 | 108 | – | 108 | 218 | 108 | 74 |
| DENv123 | 108 | 63 | 108 | 21 | 108 | 263 | 108 | 148 |
| DENv124 | 108 | 44 | 108 | 8 | 108 | 260 | 108 | 142 |
| DENv134 | 108 | 71 | 108 | 26 | 108 | 264 | 108 | 147 |
| DENv234 | 108 | 56 | 108 | 14 | 108 | 256 | 108 | 136 |
| DENv1234 | 108 | 58 | 108 | 29 | 108 | 276 | 108 | 171 |

### 5.4.2 Minimising the Risk of Hospitalisation under Consideration of Vaccine-Induced Risk

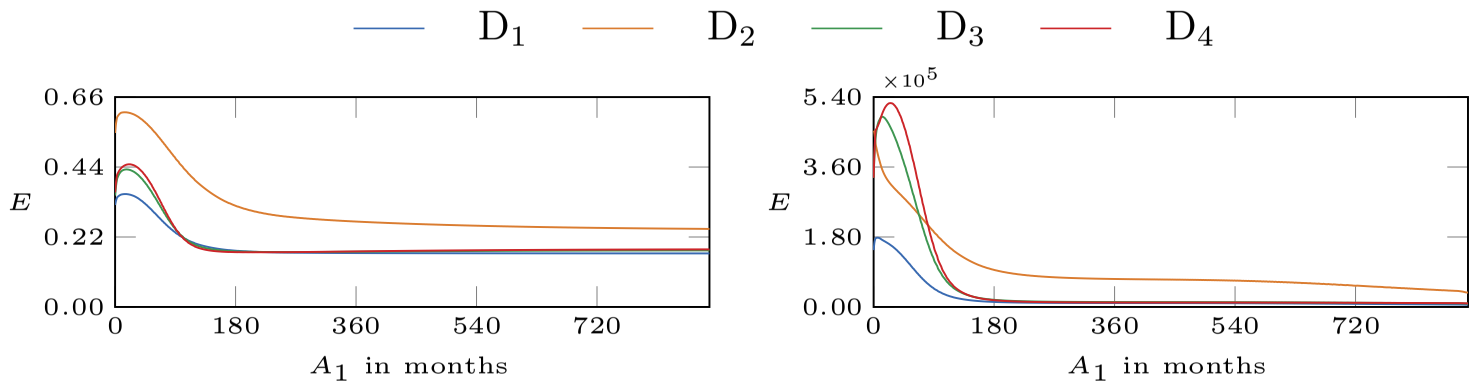
The WHO has recently revised its official recommendation for the use of Dengvaxia in endemic countries [132, 133]. The reasons for this revision were the high reported number of hospitalisations in seronegative vaccine recipients during the long-term follow-up of the Dengvaxia trials (cf. Table 1.2) and mounting pressure from the research community [4–6, 38, 74, 75]. Previously it was assumed that the application of Dengvaxia is safe in all children above 9 years of age, whereas now vaccination is recommended only for seropositives. The increased risk of hospitalisation has indeed been found to depend not only on the serostatus but also on the age of the recipient as presented in Table 1.2. In this section the vaccine-induced risk will be incorporated in the lifetime expected risk by defining the expected risk from an infection with serotype $i$ at age $a$ dependent on

the infection and vaccination history of an individual (cf. Equation (3.26)). The different CRSs need to be considered carefully as explained in Section 3.5.

A vaccine-induced risk is bound to have an impact on the optimal vaccination age for dengue. It is considered in this section for an age-dependent biting rate. Again all CRSs will be discussed in detail for any number and combination of serotypes for a constant vaccine efficacy. Further an age-dependent efficacy will be considered and results presented for all scenarios but only briefly discussed in more detail for a single serotype in circulation. The vaccine-induced risk is also assumed to be age-dependent in this case but constant if the vaccine efficacy is constant. As before, the vaccination age will then be restricted to be between 9 and 45 years according to the licence of the vaccine in Brazil in order to determine the ideal vaccination age under this constraint.

### Constant Vaccine Efficacy and Vaccine-Induced Risk

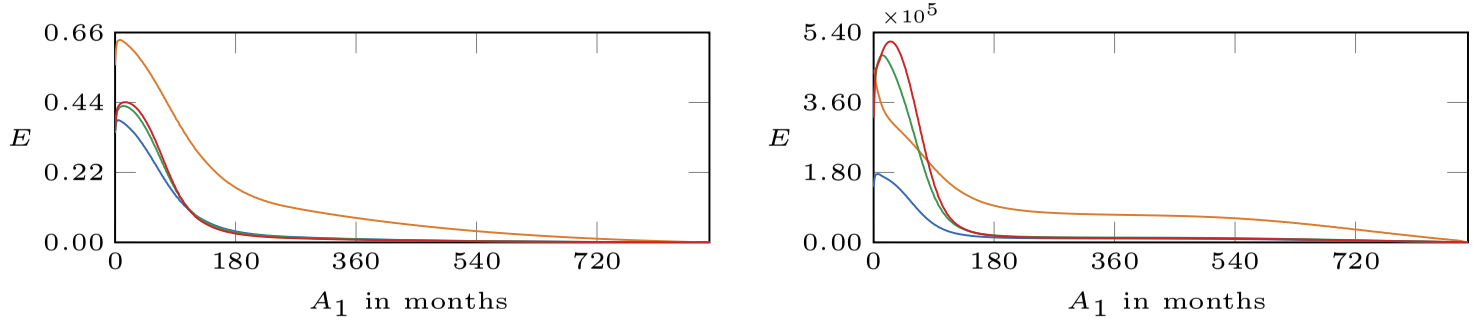
A region with only a single endemic serotype is considered initially in order to understand the effect of the vaccine-induced risk more easily. Figure 5.7 shows the lifetime expected risk due to any serotype in this case where again Figures 5.7a to 5.7d correspond to the four CRSs respectively. In comparison to Figure 5.2 it is apparent that the vaccine-induced risk significantly impacts the outcome of vaccination. In fact, if there is only a single circulating serotype vaccination is almost never recommended. The only case in which it is recommended is if either DENv3 or DENv4 is endemic in CRS (a). Considering a vaccine-induced hospitalisation risk particularly in seronegative recipients according to Table 1.2 with only a single endemic serotype means that if vaccination is successful against any non-endemic serotype prior to the natural infection the natural infection will be associated with an increased risk. The probability of successfully vaccinating against a non-endemic serotype is higher than that of vaccinating against the serotype in circulation so that this is a very likely scenario. It is therefore best not to vaccinate at all in almost all cases and clearly if primary infections are risk-free as in CRS (b) and CRS (d) since the lifetime expected risk is zero. In CRS (a) it is still beneficial to vaccinate against DENv3 or DENv4 since the vaccine is more effective against these two serotypes than against DENv1 and DENv2. It is therefore more likely that vaccination will be successful against the endemic serotype. In this case there is a trade-off between preventing some natural infections and causing too many with an increased risk due to successful vaccination against another serotype. It is therefore best to wait until some infections have occurred and only vaccinate at 258 and 206 months for DENv3 and DENv4 respectively.




(a) Vaccination is not recommended for DENv1 and DENv2. The optimal vaccination ages for DENv3 and DENv4 are 258 and 206 months respectively.




(c) Vaccination is not recommended for any serotype.




(b) Vaccination is not recommended for any serotype.




(d) Vaccination is not recommended for any serotype.

Figure 5.7: The lifetime expected risk $E$ of hospitalisation in an endemic area where a single serotype exists as a function of age $A_1$ at which the first vaccine dose is administered. The vaccine efficacy is assumed serotype-specific but age-independent as given in Table 1.1. An age-independent vaccine-induced risk is considered as given in Table 1.2. The subfigures (a)–(d) correspond to the CRS (a)–(d) respectively.

From Figure 5.7 the lifetime expected risk in the absence of vaccination in each CRS can be deduced from that of very high vaccination ages. Clearly it can therefore be seen that vaccination increases the lifetime expected risk particularly at young vaccination ages independent of the CRS. In CRS (b) and CRS (d) as shown in Figures 5.7b and 5.7d there is zero risk without vaccination and even if there is not assumed to be a difference between naturally acquired antibodies and vaccine-induced antibodies vaccination is not recommended. From Figures 5.7a and 5.7c it can be seen that vaccination also increases the lifetime expected risk in CRS (a) and CRS (c) when the vaccine induces an increased risk in subsequent infections for all serotypes at almost all vaccination ages. However, for DENv3 and DENv4 this is not the case for every vaccination age so that vaccination is recommended. Figure 5.7a shows that after the optimal vaccination age is reached the lifetime expected risk due to these serotypes hardly changes. Vaccination therefore still has very little effect when only DENv3 or DENv4 is endemic since even though some infections can be prevented at the optimal vaccination age some other infections will be associated with a higher risk.

Interestingly the shape of the lifetime expected risk is similar for each of the serotypes in CRS (a) and CRS (b) and in CRS (c) and CRS (d) respectively. In particular in CRS (a) and CRS (b) the highest lifetime expected risk is due to DENv2 and the lowest at young ages due to DENv1. DENv3 and DENv4 cause a similar lifetime expected risk independent of vaccination age. DENv1 has the highest effective reproduction number and therefore the lowest average age of infection while DENv2 has the lowest effective reproduction number and therefore the highest average age of infection. Considering that DENv2 causes a higher lifetime expected risk even though the lower effective reproduction number corresponds to fewer cases it can be deduced that more infections with DENv2 occur at high-risk ages. In CRS (c) and CRS (d) the highest lifetime expected risk at young vaccination ages is due to DENv3 and DENv4. DENv2 only causes the highest risk at older vaccination ages. In these scenarios successful vaccination against at least two serotypes means that even if an infection occurs after the vaccine was administered it is no longer risky. Therefore the lifetime expected risk is determined due to a combination of the effective reproduction number of the endemic serotype and the efficacy of the vaccine against all serotypes. The higher probability of successful vaccination against two non-endemic serotypes in combination with the low effective reproduction number therefore results in a lower lifetime expected risk caused by DENv2 at young vaccination ages than DENv3 or DENv4 in this case.

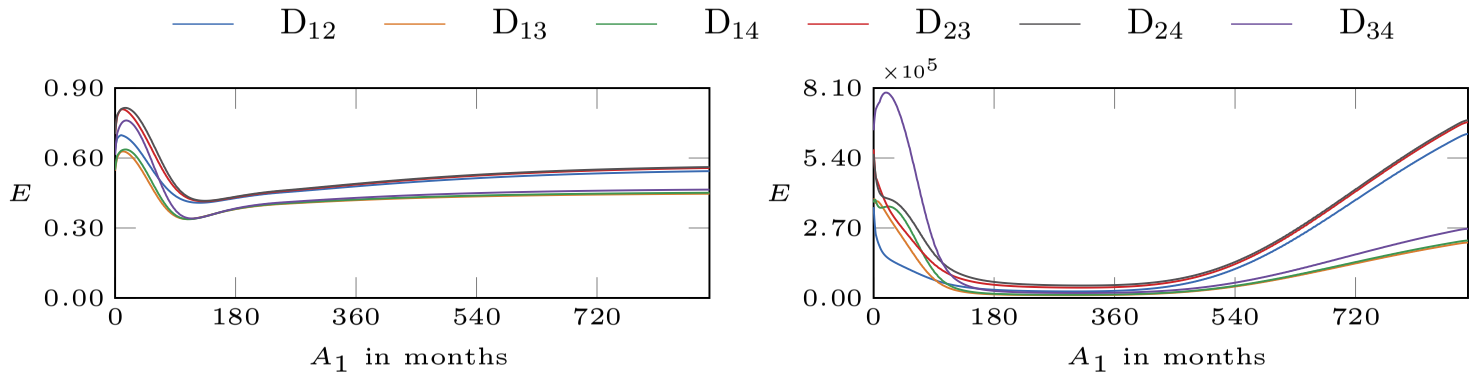
From considering a single endemic serotype it can thus be seen that if success-

ful vaccination induces a higher risk in subsequent infections with a heterologous serotype vaccination is highly likely to have a negative effect. Even in CRS (a) when only DENv3 or DENv4 is endemic and vaccination is indeed recommended the effect is only minimal and it is possible that it is not cost-effective to vaccinate. If only very few infections that result in hospitalisation can be prevented the cost of a large-scale vaccination campaign might be too high to justify. However, the question is whether with several coexisting serotypes this is still the case.

The results for an area with two endemic serotypes are presented in Figure 5.8. Considering that the vaccine-induced risk is mainly observed in seronegative recipients the presence of more than one serotype means that vaccination may be more beneficial. This is the case if it is carried out after most primary infections have occurred to ensure a high proportion of seropositive recipients.

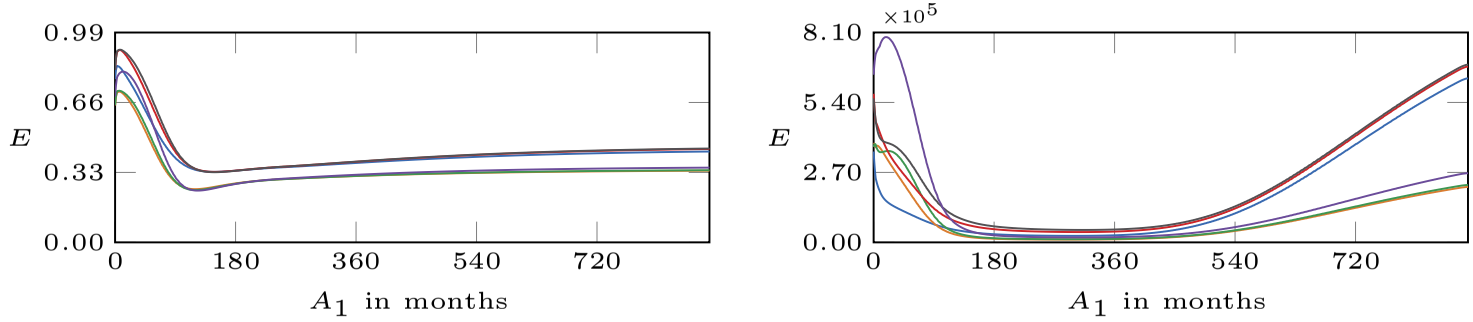
CRS (a) is considered in Figure 5.8a. In fact vaccination is now recommended despite the vaccine-induced risk at optimal vaccination ages between 108 and 135 months. However, clearly there is still a very negative effect if vaccination takes place at young ages when most individuals are seronegative. This can again be deduced by noting that the lifetime expected risk for very high vaccination ages tends to the lifetime expected risk in the absence of vaccination. Serotype combinations with DENv1 at young ages lead to a lower lifetime expected risk which is possibly due to the high effective reproduction number and the associated risk at the average age of infection being lower than for the remaining serotypes. At older vaccination ages serotype combinations with DENv2 cause a higher risk than those without this serotype. The reason for this is the combination of the lower effective reproduction number and the higher average age of infection as well as the low efficacy against this serotype meaning that fewer infections can be prevented. For combinations with DENv2 the optimal vaccination ages are also slightly higher since the higher average age of infection means it is necessary to delay the start of the vaccination campaign longer in order to vaccinate fewer seronegative recipients.

In CRS (b) as shown in Figure 5.8b the observations are in fact very similar to CRS (a). Considering that primary infections are not targeted in CRS (a) so as to prevent the vaccination of seronegative individuals this is to be expected. In CRS (b) vaccinating before a primary infection would not be necessary even if there was no vaccine-induced risk. With the vaccine-induced risk vaccinating before most primary infections take place only has a negative impact so that it is crucial to start the vaccination campaign at ages when most individuals have had exactly one infection. The optimal vaccination ages are therefore similar to those




(a) The optimal vaccination ages for DENv12, DENv13, DENv14, DENv23, DENv24 and DENv34 are 126, 108, 111, 133, 135 and 116 months respectively.

(c) The optimal vaccination ages for DENv12, DENv13, DENv14, DENv23, DENv24 and DENv34 are 298, 289, 293, 307, 311 and 307 months respectively.




(b) The optimal vaccination ages for DENv12, DENv13, DENv14, DENv23, DENv24 and DENv34 are 147, 119, 120, 149, 149 and 123 months respectively.

(d) The optimal vaccination ages for DENv12, DENv13, DENv14, DENv23, DENv24 and DENv34 are 298, 289, 293, 307, 311 and 307 months respectively.

Figure 5.8: The lifetime expected risk $E$ of hospitalisation in an endemic area where two serotypes coexist as a function of age $A_1$ at which the first vaccine dose is administered. The vaccine efficacy is assumed serotype-specific but age-independent as given in Table 1.1. An age-independent vaccine-induced risk is considered as given in Table 1.2. The subfigures (a)–(d) correspond to the CRS (a)–(d) respectively.

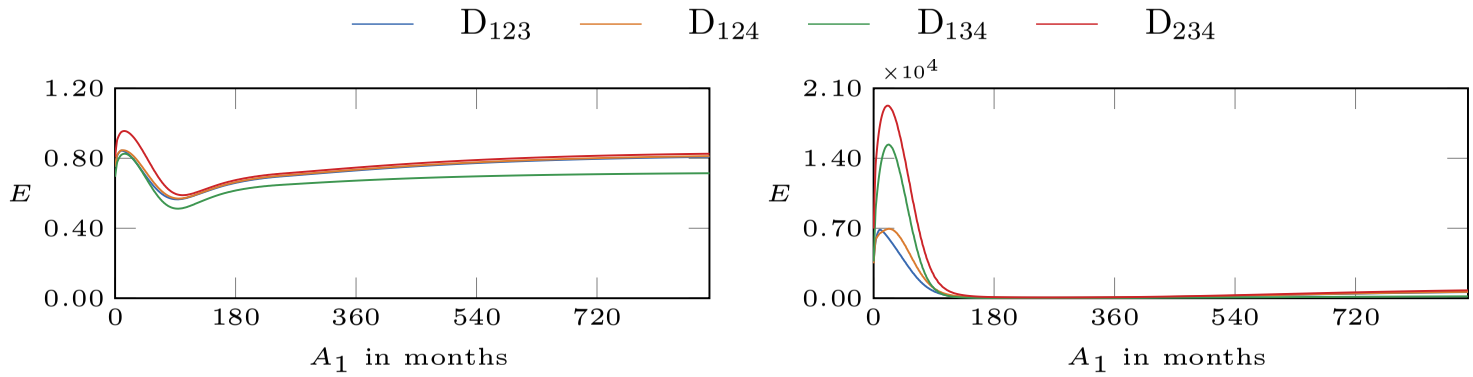
obtained in CRS (a), between 119 and 149 months with higher optimal vaccination ages for combinations including DENv2. In CRS (a) the optimal vaccination ages are slightly lower since it is still possible to prevent some primary infections which are risky without necessarily causing an increased risk in post-vaccination infections.

CRS (c) and CRS (d) are presented in Figures 5.8c and 5.8d respectively. In CRS (c) primary infections are risky while they are risk-free in CRS (d). However, vaccinating seronegatives is not the ideal approach in either case so that this assumption does not have any impact on the lifetime expected risk and optimal vaccination age. In both these CRSs it is therefore best to vaccinate after a primary infection but before a secondary infection. If vaccination is then successful against at least one of the serotypes the individual was not infected with they will no longer be at any risk due to dengue. The lifetime expected risk can be drastically reduced for vaccination ages between 180 and 400 months in both CRSs. The ideal time to vaccinate is between 289 and 311 months. However, if vaccination is delayed even further and most secondary infections have already taken place vaccination has much less effect and the lifetime expected risk can no longer be significantly reduced. Interestingly assuming that two heterologous infections confer PCI vaccination at any age actually reduces the lifetime expected risk for serotype combinations including DENv2 despite the vaccine inducing a higher risk in seronegative recipients that have a subsequent infection with a serotype they were not successfully vaccinated against. This is particularly obvious for DENv12. In comparison to DENv3 and DENv4 the vaccine is fairly ineffective against DENv1 and DENv2. DENv2 further has a high average age of infection due to its low effective reproduction number while the average age of infection of DENv1 is lower. For this combination it is therefore likely that vaccination is successful against the two non-endemic serotypes so that even if seronegatives are vaccinated the risk can be reduced. In the case of the vaccine being effective against only one of the non-endemic serotypes the infection sequence following vaccination is most likely to be DENv1 and then DENv2. Infections with DENv1 occur at lower risk ages and the infection caused by DENv2 will be a post-secondary type infection and therefore free of risk. The highest increase in lifetime expected risk at young ages compared to without any vaccination is observed for DENv34. In this case it is most likely that the vaccine will be effective against one of the endemic serotypes but not necessarily against any non-endemic serotype. Since most individuals will be seronegative at these young vaccination ages the subsequent natural infection will be risky as it is a secondary type infection

and due to the successful vaccination of a seronegative this risk will be further increased.

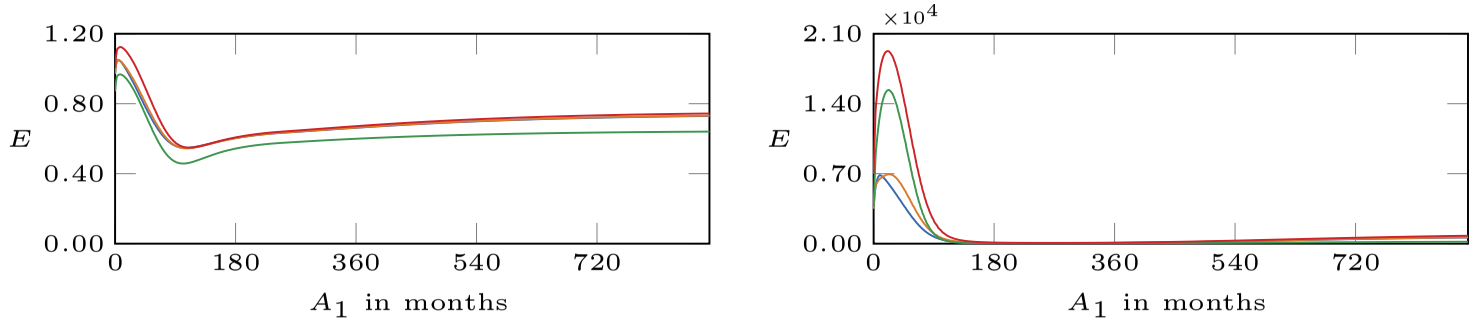
By studying an endemic area with two coexisting serotypes it can therefore be seen that if the vaccine induces a higher risk in breakthrough infections in seronegative recipients the assumption of primary infection being risk-free or risky does not make a significant difference. However, the optimal vaccination age is very different depending on whether or not we assume PCI after two heterologous infections.

Figures 5.9 and 5.10 show the lifetime expected risk in an endemic area with three and four co-circulating serotypes respectively. Again the subfigures correspond to the different CRSs. The observations for CRS (a) and CRS (b) for several coexisting serotypes are very similar to the case of two endemic serotypes. However, in comparison to two serotypes the optimal vaccination ages in CRS (a) are slightly lower, between 94 and 101 months for three serotypes and 77 months for all four serotypes coexisting. Similarly in CRS (b) the optimal vaccination ages are lower, between 102 and 111 months for three endemic serotypes and 91 months for all serotypes. This increase is due to a the higher combined effective reproduction number for more coexisting serotypes and the associated decrease in average age of infection. Primary infections therefore occur earlier and vaccination is ideal at slightly younger ages. This can similarly be observed in CRS (c) and CRS (d) with the optimal vaccination age between 248 and 265 months for three coexisting serotypes and at 156 months for all four serotypes coexisting. In CRS (c) compared to CRS (d) there is again no effect due to primary infections being risk-free and the optimal vaccination age is unchanged. However, contrary to the case of two coexisting serotypes there is no longer any serotype combination for which the lifetime expected risk can be reduced at any vaccination age in these CRSs. In fact, vaccinating early increases the risk drastically independent of the serotype combination. If vaccination is only successful against a single serotype there is a higher probability of a subsequent infection having a vaccine-induced risk due to more serotypes coexisting. The average age of infection is further affected in such a way that infections that do occur are riskier particularly if DENv2 is endemic. If vaccination takes place after most secondary infections occur the lifetime expected risk is again higher since less infections can be prevented. However, at these high vaccination ages only very few seronegatives will be vaccinated so that the vaccine-induced risk does not drastically increase the lifetime expected risk.




(a) The optimal vaccination ages for DENv123, DENv124, DENv134 and DENv234 are 94, 95, 94 and 101 months respectively.

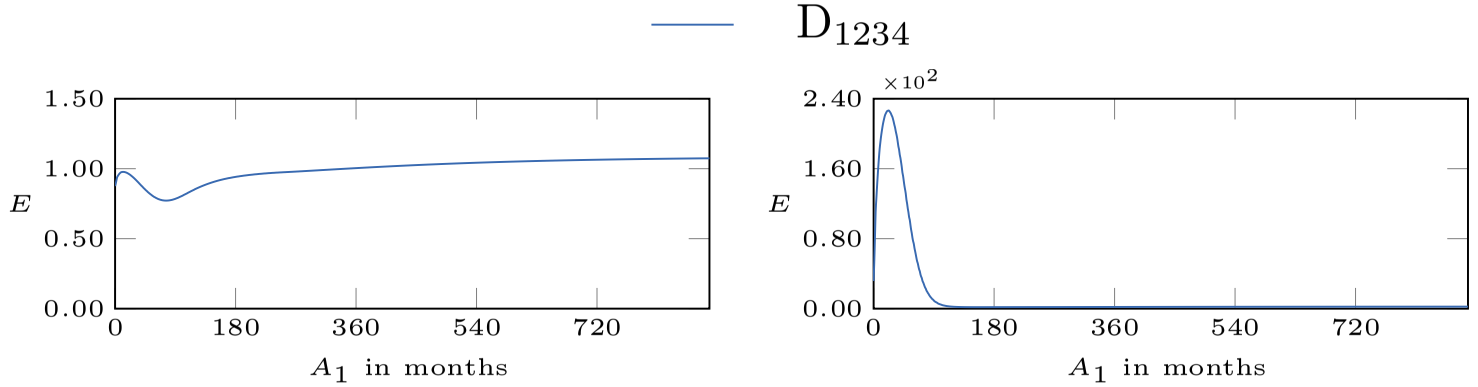
(c) The optimal vaccination ages for DENv123, DENv124, DENv134 and DENv234 are 248, 254, 238 and 265 months respectively.




(b) The optimal vaccination ages for DENv123, DENv124, DENv134 and DENv234 are 106, 108, 102 and 111 months respectively.

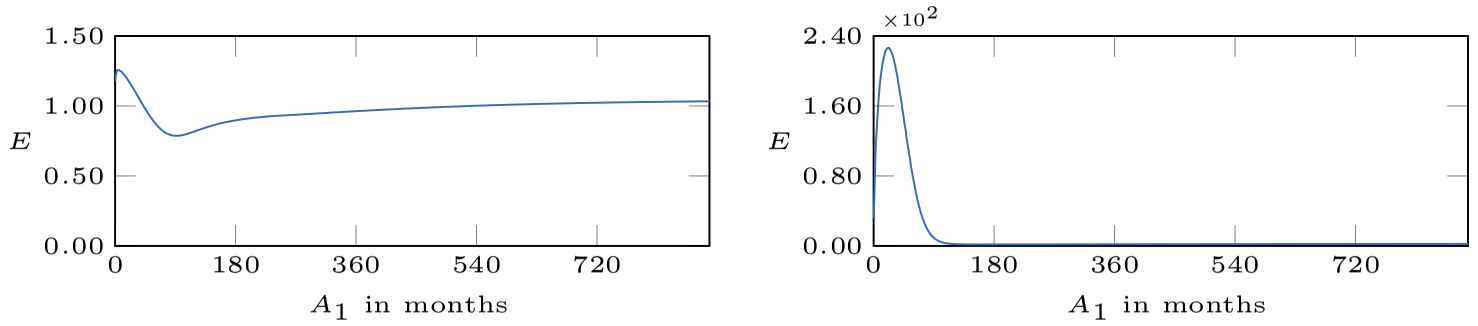
(d) The optimal vaccination ages for DENv123, DENv124, DENv134 and DENv234 are 248, 254, 238 and 265 months respectively.

Figure 5.9: The lifetime expected risk $E$ of hospitalisation in an endemic area where three serotypes coexist as a function of age $A_1$ at which the first vaccine dose is administered. The vaccine efficacy is assumed serotype-specific but age-independent as given in Table 1.1. An age-independent vaccine-induced risk is considered as given in Table 1.2. The subfigures (a)–(d) correspond to the CRS (a)–(d) respectively.




(a) The optimal vaccination age for DENv1234 is 77 months.

(c) The optimal vaccination age for DENv1234 is 156 months.




(b) The optimal vaccination age for DENv1234 is 91 months.

(d) The optimal vaccination age for DENv1234 is 156 months.

Figure 5.10: The lifetime expected risk $E$ of hospitalisation in an endemic area where all four serotypes coexist as a function of age $A_1$ at which the first vaccine dose is administered. The vaccine efficacy is assumed serotype-specific but age-independent as given in Table 1.1. An age-independent vaccine-induced risk is considered as given in Table 1.2. The subfigures (a)–(d) correspond to the CRS (a)–(d) respectively.

Table 5.6: The optimal vaccination age $A_1$ in months which minimises the lifetime expected risk $E$ of hospitalisation for all CRSs. The vaccine efficacy is assumed serotype-specific but age-independent as given in Table 1.1. An age-independent vaccine-induced risk is considered as given in Table 1.2. '–' represents cases in which vaccination is not recommended, i.e. when $A_1$ was found to be above a reasonable age for humans.

| | CRS (a) | | CRS (b) | | CRS (c) | | CRS (d) | |
|---|---|---|---|---|---|---|---|---|
| | $A_1$ | $E_{\times 10^{-2}}$ | $A_1$ | $E_{\times 10^{-2}}$ | $A_1$ | $E_{\times 10^{0}}$ | $A_1$ | $E_{\times 10^{0}}$ |
| DENv1 | – | 16.84 | – | 0.00 | – | 5,703 | – | 0.00 |
| DENv2 | – | 24.54 | – | 0.00 | – | 37,169 | – | 0.00 |
| DENv3 | 258 | 17.25 | – | 0.00 | – | 8,780 | – | 0.00 |
| DENv4 | 206 | 17.20 | – | 0.00 | – | 9,296 | – | 0.00 |
| DENv12 | 126 | 40.81 | 147 | 33.26 | 298 | 25,204 | 298 | 25,203 |
| DENv13 | 108 | 33.81 | 119 | 25.11 | 289 | 10,679 | 289 | 10,678 |
| DENv14 | 111 | 33.77 | 120 | 24.69 | 293 | 12,223 | 293 | 12,223 |
| DENv23 | 133 | 41.44 | 149 | 33.26 | 307 | 39,766 | 307 | 39,765 |
| DENv24 | 135 | 41.66 | 149 | 33.10 | 311 | 48,007 | 311 | 48,007 |
| DENv34 | 116 | 34.08 | 123 | 24.43 | 307 | 19,181 | 307 | 19,181 |
| DENv123 | 94 | 56.53 | 106 | 54.75 | 248 | 45.59 | 248 | 45.56 |
| DENv124 | 95 | 56.97 | 108 | 54.46 | 254 | 50.91 | 254 | 50.88 |
| DENv134 | 94 | 51.20 | 102 | 45.80 | 238 | 19.81 | 238 | 19.79 |
| DENv234 | 101 | 58.89 | 111 | 54.89 | 265 | 75.17 | 265 | 75.14 |
| DENv1234 | 77 | 77.20 | 91 | 78.69 | 156 | 1.69 | 156 | 1.68 |

The optimal vaccination ages together with the minimal lifetime expected risk for an age-independent efficacy and an age-independent vaccine-induced risk are presented in Table 5.6. It can clearly be seen that the optimal vaccination age mainly depends on the assumption of PCI while assuming risk-free infections has hardly any effect in CRS (b) compared to CRS (a) and even less in CRS (d) compared to CRS (c). It can further be noted that the lifetime expected risk is far higher in CRS (c) and CRS (d) than in CRS (a) and CRS (b) even though more infections are risky in the latter scenarios. However, the lifetime expected risk is in fact not comparable across the different CRSs. The vaccine-induced risk was introduced in such a way that the risk, as measured in the pre-vaccine era, was attributed to only those infections that are risky. The vaccine-induced risk then leads to a substantial increase in lifetime expected risk especially if post-secondary infections are assumed risk-free.

Vaccination in endemic areas with a single circulating serotype is only recommended in CRS (a) when either DENv3 or DENv4 is endemic. In all other cases the vaccine-induced risk in seronegative recipients results in vaccination being coun-

terproductive. In CRS (a) and CRS (b) it is ideal to vaccinate after most primary infections. However, it can still be beneficial to vaccinate some seronegatives in CRS (a) since this makes it possible to prevent risky primary infections. The optimal vaccination ages between 77 and 135 months for several coexisting serotypes in CRS (a) are therefore lower than in CRS (b) (between 91 and 149 months). In CRS (c) and CRS (d) vaccination can prevent all risky infections if it is successful against any serotype a seropositive individual was not infected with. It is therefore better to vaccinate when almost all primary infections have occurred even if that means some secondary infections can no longer be prevented. The optimal vaccination ages in CRS (c) and CRS (d) are therefore identical since the only difference is the risk of primary infections that should ideally already have taken place. They are between 156 and 311 months and therefore much higher than in CRS (a) and CRS (b).

Overall it is therefore very important to determine whether PCI is indeed conferred by two heterologous infections. A vaccine-induced risk is likely due to ADE. Risk-free primary infections are based on this phenomenon since often secondary infections are more risky than primary infection. Considering this the optimal vaccination ages obtained in CRS (b) and CRS (d) are more realistic. However, the vaccination ages obtained in CRS (a) and CRS (c) are very similar so that it is in fact not relevant whether primary infection are indeed risk-free due to ADE if the vaccine induces a higher risk in seronegatives. The number of serotypes is also relevant for the optimal vaccination strategy since the average age of infection for dengue overall reduces as the number of serotypes increases so that the age at which a significant proportion of individuals will be seropositive is reached earlier.

### Age-Dependent Vaccine Efficacy and Vaccine-Induced Risk

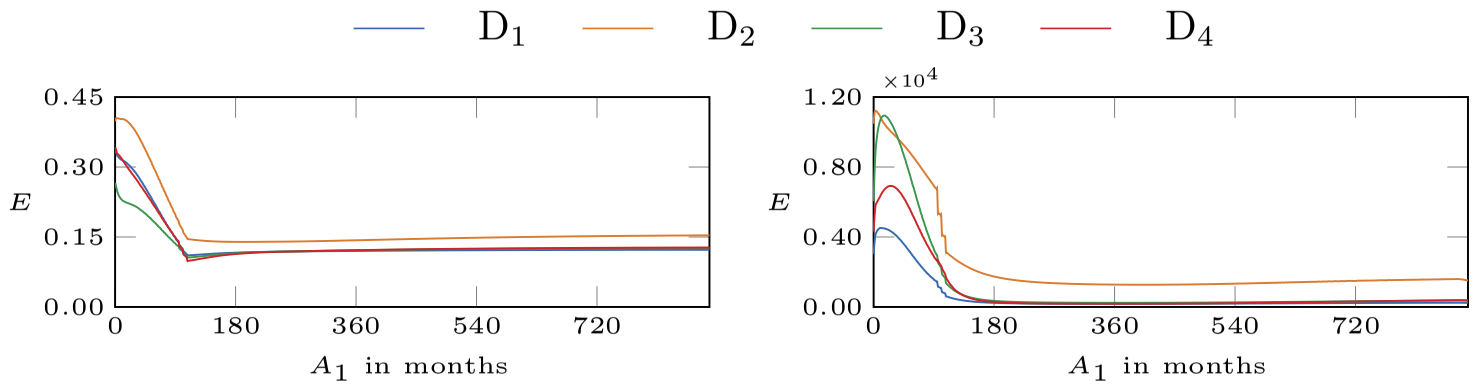
The results for an age-dependent efficacy as was observed in the Dengvaxia trials [32, 66] are presented in Table 5.7 for all CRSs. Based on these age-groups the numbers of hospitalisations for seronegative and seropositive recipients in the control and vaccine group in the long-term follow-up were also observed to be different (cf. Table 1.2). Therefore the effect of both an age-dependent efficacy and an age-dependent vaccine-induced risk will be considered next.

For a single serotype in circulation the lifetime expected risk caused by each of the serotypes is presented in Figure 5.11 where again Figures 5.11a to 5.11d correspond to CRS (a)–(d). Similarly to the case of hospitalisation where no vaccine-induced risk was considered the assumption of an age-dependent efficacy results

in drops of the lifetime expected risk when one or more doses are administered in the older age-group, i.e. at 96, 102 and 108 months for all CRSs. These drops are most obvious for DENv2 in CRS (c) and CRS (d). However, in general the effect is not particularly pronounced. This is due to the fact that vaccination of seronegatives has a negative impact, however with an increasing age the probability of vaccinating seronegatives decreases. Hence the higher efficacy which would intuitively lead to more infections with a vaccine-induced risk is balanced out by the fact that more seropositives are vaccinated. Additionally to the increase in efficacy there is a decrease in vaccine-induced risk at 9 years of age. The combination of this results in vaccination being recommended when primary infections are risky, i.e. in CRS (a) and CRS (c), which was not the case for all scenarios with an age-independent efficacy and vaccine-induced risk. In particular the optimal vaccination age is between 108 and 190 months in CRS (a) and much higher, between 360 and 407 months, in CRS (c). From Figures 5.11a and 5.11c it can, however, be seen that vaccination has a very limited effect similarly to those two cases that required vaccination with a constant vaccine efficacy. Since primary infections are

Table 5.7: The optimal vaccination age $A_1$ in months which minimises the lifetime expected risk $E$ of hospitalisation for all CRSs. The vaccine efficacy is assumed serotype-specific and age-dependent as given in Table 1.1. An age-dependent vaccine-induced risk is considered as given in Table 1.2. '–' represents cases in which vaccination is not recommended, i.e. when $A_1$ was found to be above a reasonable age for humans.

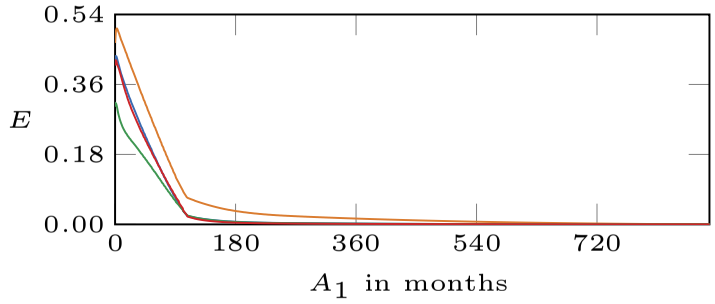
| | CRS (a) | | CRS (b) | | CRS (c) | | CRS (d) | |
|---|---|---|---|---|---|---|---|---|
| | $A_1$ | $E_{\times 10^{-2}}$ | $A_1$ | $E_{\times 10^{-2}}$ | $A_1$ | $E_{\times 10^{0}}$ | $A_1$ | $E_{\times 10^{0}}$ |
| DENv1 | 108 | 11.05 | – | 0.00 | 363 | 181.6 | – | 0.00 |
| DENv2 | 190 | 13.95 | – | 0.00 | 407 | 1,269 | – | 0.00 |
| DENv3 | 108 | 10.58 | – | 0.00 | 371 | 237.9 | – | 0.00 |
| DENv4 | 108 | 9.87 | – | 0.00 | 360 | 179.8 | – | 0.00 |
| DENv12 | 108 | 35.14 | 323 | 41.83 | 289 | 16,060 | 289 | 16,060 |
| DENv13 | 108 | 29.13 | 138 | 30.36 | 280 | 6,752 | 280 | 6,752 |
| DENv14 | 108 | 28.13 | 121 | 28.13 | 285 | 8,849 | 285 | 8,849 |
| DENv23 | 108 | 34.38 | 283 | 42.00 | 298 | 25,011 | 298 | 25,011 |
| DENv24 | 108 | 33.35 | 263 | 41.42 | 307 | 37,607 | 307 | 37,607 |
| DENv34 | 108 | 27.69 | 119 | 26.71 | 298 | 13,801 | 298 | 13,801 |
| DENv123 | 108 | 54.89 | 268 | 69.87 | 230 | 32.74 | 230 | 32.69 |
| DENv124 | 108 | 54.44 | 242 | 68.87 | 241 | 40.10 | 241 | 40.05 |
| DENv134 | 108 | 48.71 | 125 | 53.29 | 224 | 15.81 | 224 | 15.76 |
| DENv234 | 108 | 54.81 | 173 | 67.59 | 256 | 58.21 | 256 | 58.16 |
| DENv1234 | 108 | 79.59 | 148 | 88.85 | 148 | 1.66 | 147 | 1.63 |



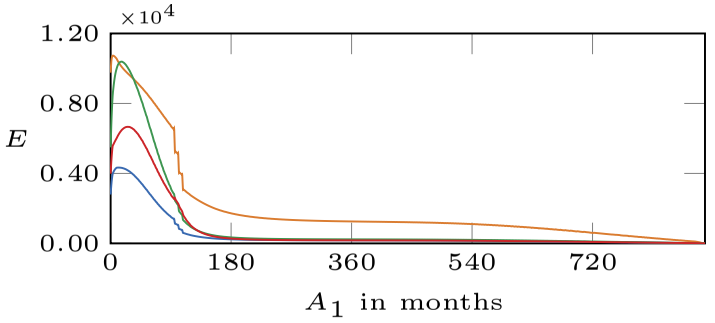

(a) The optimal vaccination ages for DENv1, DENv2, DENv3 and DENv4 are 108, 190, 108 and 108 months respectively.




(c) The optimal vaccination ages for DENv1, DENv2, DENv3 and DENv4 are 363, 407, 371 and 360 months respectively.




(b) Vaccination is not recommended for any serotype.




(d) Vaccination is not recommended for any serotype.

Figure 5.11: The lifetime expected risk $E$ of hospitalisation in an endemic area where a single serotype exists as a function of age $A_1$ at which the first vaccine dose is administered. The vaccine efficacy is assumed serotype-specific and age-dependent as given in Table 1.1. An age-dependent vaccine-induced risk is considered as given in Table 1.2. The subfigures (a)–(d) correspond to the CRS (a)–(d) respectively.

risky there is therefore again a trade-off between vaccinating some seronegatives successfully against the endemic serotype and risking a vaccine-induced risk if vaccination is successful against any non-endemic serotype. For several coexisting serotypes the observations are very similar and the corresponding figures are therefore omitted.

The minimal lifetime expected risk and corresponding optimal vaccination age for any number and combination of serotypes when an age-dependent efficacy and age-dependent vaccine-induced risk are considered is presented in Table 5.7. Comparing the results to those for a constant efficacy and pooled vaccine-induced risk as summarised in Table 5.6 it is clear that in CRS (c) and CRS (d) there is a very limited effect on the optimal vaccination age for several coexisting serotypes. The ages are more influenced by the overall effective reproduction number of the circulating serotypes and the average age of infection than the efficacy of the vaccine in these scenarios. However, the minimal lifetime expected risk is much lower due to the higher efficacy at the ideal vaccination age when the age-groups are considered. The higher efficacy when considering age-groups also results in some of the vaccination ages being slightly reduced in comparison to the constant efficacy case since a few more infections can be prevented and therefore the risk to vaccinate a few more seronegatives at a younger age can be taken.

In CRS (a) the optimal vaccination age is 108 months for all combinations with the exception of only DENv2 being endemic in which case it is 190 months. For a constant vaccine efficacy most vaccination ages were already fairly close to 108 months. Since the vaccine efficacy at this age increases and the vaccine-induced risk decreases it is therefore best to vaccinate at exactly 9 years instead of slightly before or after. In CRS (b) the situation is slightly different, with a significant increase in optimal vaccination age in some cases, e.g. whenever DENv2 is endemic. Only primary infections are risk-free and vaccinating seronegatives is therefore not necessary and indeed counterproductive due to the vaccine inducing a higher risk in subsequent infections. The vaccine is least effective against DENv2 and with a lower vaccine-induced risk in individuals aged above 9 years it is better to wait longer to ensure fewer seronegatives are vaccinated if this serotype is present. Interestingly in CRS (b) the minimal lifetime expected risk is higher than if the vaccine-induced risk and efficacy are assumed constant. This is due to the later vaccination ages when more primary infections will have already occurred.

Comparing the results for a constant and an age-dependent efficacy highlights how important the vaccine efficacy is. With the higher efficacy when the age-groups are considered there are cases in which vaccination can be beneficial even

if for the lower pooled efficacy at the obtained optimal vaccination age it would not be. Additionally with the age-dependent efficacy and age-dependent vaccine-induced risk it is now important whether ADE really does imply risk-free primary infections since the results for CRS (a) and CRS (b) are no longer similar. However, if there is PCI after two heterologous infections the risk of the primary infection is only relevant in endemic areas with a single serotype.

### Licence Restrictions

In the case of vaccine-induced risk many of the vaccination ages are within the permitted age-range for Dengvaxia. For an age-dependent efficacy and age-dependent vaccine-induced risk there is in fact no scenario that requires vaccination outwith the age-range of 9 to 45 years. All optimal vaccination ages in this age-dependent case are between 108 and 407 months. If the age-groups are

Table 5.8: The vaccination age $A_1$ in months which lies within the permitted age-range for the vaccine and minimises the lifetime expected risk $E$ of hospitalisation. The percentage increase from the optimal lifetime expected risk $\delta_E\%$ is given for any case in which the optimal vaccination age lies outwith the permitted age-range of Dengvaxia. For cases in which vaccination is not recommended and the minimal lifetime expected risk is zero the percentage increase is given by $\infty$. The vaccine efficacy is assumed serotype-specific but age-independent as given in Table 1.1. Correspondingly the vaccine-induced risk is considered to be age-independent as given in Table 1.2.

| | CRS (a) | | CRS (b) | | CRS (c) | | CRS (d) | |
|---|---|---|---|---|---|---|---|---|
| | $A_1$ | $\delta_E\%$ | $A_1$ | $\delta_E\%$ | $A_1$ | $\delta_E\%$ | $A_1$ | $\delta_E\%$ |
| DENv1 | 538 | $< 1$ | 538 | $\infty$ | 538 | 69 | 538 | $\infty$ |
| DENv2 | 538 | 4 | 538 | $\infty$ | 538 | 82 | 538 | $\infty$ |
| DENv3 | 258 | – | 538 | $\infty$ | 538 | 40 | 538 | $\infty$ |
| DENv4 | 206 | – | 538 | $\infty$ | 538 | 21 | 538 | $\infty$ |
| DENv12 | 126 | – | 147 | – | 298 | – | 298 | – |
| DENv13 | 108 | – | 119 | – | 289 | – | 289 | – |
| DENv14 | 111 | – | 120 | – | 293 | – | 293 | – |
| DENv23 | 133 | – | 149 | – | 307 | – | 307 | – |
| DENv24 | 135 | – | 149 | – | 311 | – | 311 | – |
| DENv34 | 116 | – | 123 | – | 307 | – | 307 | – |
| DENv123 | 108 | 2 | 108 | $< 1$ | 248 | – | 248 | – |
| DENv124 | 108 | 1 | 108 | – | 254 | – | 254 | – |
| DENv134 | 108 | 2 | 108 | $< 1$ | 238 | – | 238 | – |
| DENv234 | 108 | $< 1$ | 111 | – | 265 | – | 265 | – |
| DENv1234 | 108 | 7 | 108 | 2 | 156 | – | 156 | – |

disregarded and PCI is considered the optimal vaccination age is between 156 and 311 months. However, if the age-groups are disregarded, in CRS (a) and CRS (b) there are some vaccination ages that are below the minimum age for Dengvaxia if the efficacy and vaccine-induced risk are assumed constant. Table 5.8 therefore presents the ages at which the vaccine should be administered under the current licence restriction together with the percentage increase from the minimal lifetime expected risk for a constant efficacy and pooled vaccine-induced risk. For an age-dependent efficacy and age-dependent vaccine-induced risk the corresponding table is not shown as the optimal age adheres to the restriction and the increase is therefore 0% in all cases in which vaccination is recommended. For a single serotype and risk-free primary infections the minimal risk is zero.

The negative impact of restricting the vaccination age to be between 9 and 45 years for all three vaccination doses is very limited. As was noted previously vaccination under licence restrictions should be carried out as close to the ideal age as possible, i.e. at 9 years if it is below that age and at 45 years if it is above that age or not recommended. The highest percentage increase for cases in which vaccination is recommended is 7% when all four serotypes coexist in CRS (a). If there is only a single serotype in existence vaccination is not recommended in CRS (c). However, if vaccination is carried out the percentage increase is between 21% and 82%. The lowest increase in this case is observed for DENv4 due to the high efficacy against this serotype and similarly the highest increase for DENv2 due to the low efficacy. The lower the efficacy for the endemic serotype the more harm can therefore be caused when a vaccination campaign is carried out in an endemic region with one serotype.

If Dengvaxia causes an increased risk in seronegative recipients the licence restriction therefore has no effect if two heterologous infections confer PCI as long as the vaccine is not administered in endemic regions with only one serotype. If there is no PCI and the vaccine efficacy and the induced risk are constant the increase in lifetime expected risk is very limited. If the efficacy and vaccine-induced risk are age-dependent the optimal ages are already in accordance with the licence. The licence restriction is therefore much less problematic if the vaccine indeed causes an increased risk in seronegative recipients as was observed in the long-term follow-up of the Dengvaxia trials.

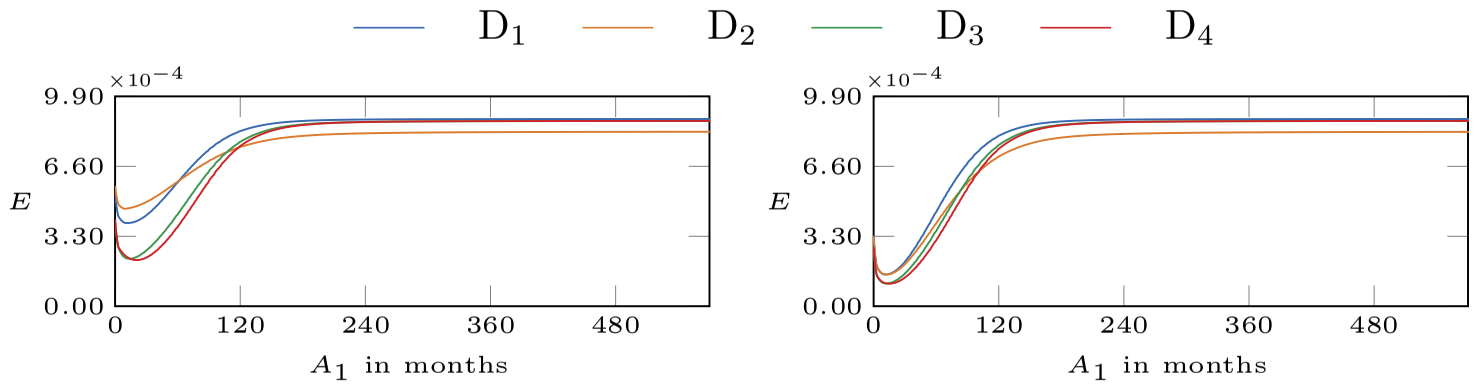
### 5.4.3 Minimising the Risk of Lethality

In the model with a constant rate for the death of humans and a constant mosquito biting rate there was a significant difference depending on whether hospitalisation or lethality was targeted by vaccination. The two risk functions are in fact very similar with peaks at young ages and an increasing risk in the population aged above 60 years. However, the risk for lethality at all ages is far below that of requiring hospital treatment. As most cases that result in the death of the patient will have been treated in a hospital this is not surprising. The biggest difference between the risk functions is that the risk at old ages compared to the peak at young ages is far higher in lethality. This is caused by the age of the patients and possible underlying health issues that are more relevant at old age. Assuming a step-death function where every human dies at the age of 73.8 years is likely to weaken this effect significantly. In addition to this cut-off, the force of infection is now age-dependent due to the age-dependent biting rate. It is very low for those high ages which will further dampen the impact of the high risk associated with old age as the probability of getting infected is lowered. The expectation when considering the risk of lethality as opposed to that of hospitalisation in the case of an age-dependent biting rate and a step-death function is therefore that optimal vaccination ages will be much more similar.

There is no data available so far that shows an increased risk of lethality in vaccinated individuals. The expected risk of an infection with serotype $i$ at age $a$ in this section will therefore only be based on the infection history of the individual and vaccination will be considered to correspond to a silent natural infection. Again results will be presented for a constant and an age-dependent vaccine efficacy and the effect of the age-restriction of the licence will be discussed. However, since the age-dependent biting rate and step-death function result in very little difference between targeting the risk of hospitalisation or lethality the discussion of these results will be kept short.

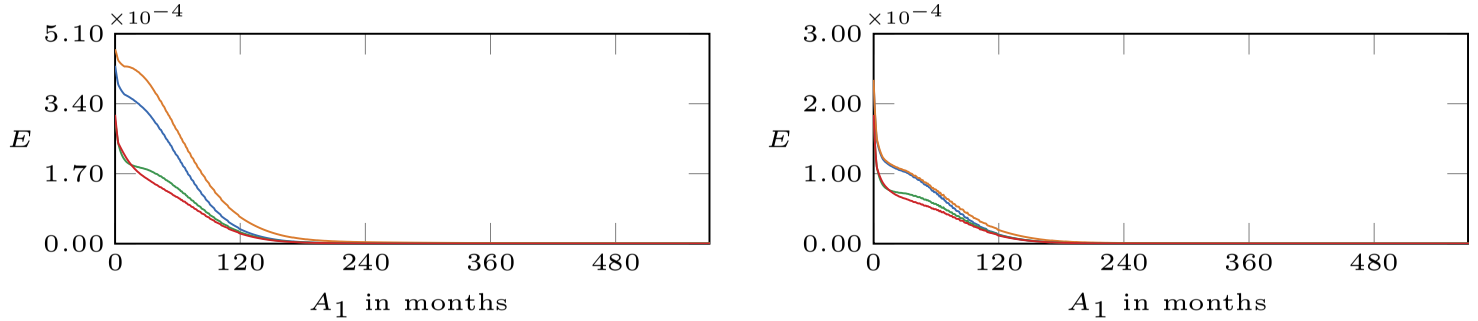
#### Constant Vaccine Efficacy

The lifetime expected risk of lethality for endemic regions with a single serotype is presented in Figure 5.12. By comparing this to Figure 5.2 one can see that indeed very little difference exists between the two risk functions independent of the CRS. This is caused by the age-dependence of the biting rate and the step-death function. All observations made for the risk of hospitalisation without any vaccine-induced risk are therefore transferable to the risk of lethality. For example one important factor in determining the lifetime expected risk is the ef-




(a) The optimal vaccination ages for DENv1, DENv2, DENv3 and DENv4 are 11, 9, 14 and 20 months respectively.

(c) The optimal vaccination ages for DENv1, DENv2, DENv3 and DENv4 are 11, 11, 12 and 14 months respectively.




(b) Vaccination is not recommended for any serotype.

(d) Vaccination is not recommended for any serotype.

Figure 5.12: The lifetime expected risk $E$ of lethality in an endemic area where a single serotype exists as a function of age $A_1$ at which the first vaccine dose is administered. The vaccine efficacy is assumed serotype-specific but age-independent as given in Table 1.1. The subfigures (a)–(d) correspond to the CRS (a)–(d) respectively.

ficacy of the vaccine against endemic serotypes in CRS (a) and CRS (b). In CRS (c) and CRS (d) there are less differences between the four serotypes since successful vaccination against two non-endemic serotypes can reduce the risk and therefore a combination of the overall vaccine efficacy and the effective reproduction number of the endemic serotype determine the risk. Clearly with risk-free primary infections there is zero risk if only a single serotype is endemic and hence vaccination is again not recommended if the risk is lethality. The observations for any number and combination of serotypes are similarly transferable so that figures for several coexisting serotypes when the risk of lethality is targeted are omitted. The only difference to the risk of hospitalisation is the much lower lifetime expected risk due to the fact that fewer infections are fatal than require hospital treatment.

The optimal vaccination age and minimal lifetime expected risk for all scenarios and any combination of serotypes is shown in Table 5.9. Again the conclusions drawn for hospitalisation apply to lethality as well. However, in some cases the risk of lethality is minimised for slightly younger vaccination ages than the risk of hospitalisation. This is due to the fact that the highest risk of death in children is observed shortly before the peak of hospitalisations is reached. The

Table 5.9: The optimal vaccination age $A_1$ in months which minimises the lifetime expected risk $E$ of lethality for all CRSs. The vaccine efficacy is assumed serotype-specific but age-independent as given in Table 1.1. '–' represents cases in which vaccination is not recommended, i.e. when $A_1$ was found to be above a reasonable age for humans.

| | CRS (a) | | CRS (b) | | CRS (c) | | CRS (d) | |
|---|---|---|---|---|---|---|---|---|
| | $A_1$ | $E_{\times 10^{-4}}$ | $A_1$ | $E_{\times 10^{-4}}$ | $A_1$ | $E_{\times 10^{-4}}$ | $A_1$ | $E_{\times 10^{-4}}$ |
| DENv1 | 11 | 3.93 | – | 0.00 | 11 | 1.50 | – | 0.00 |
| DENv2 | 9 | 4.59 | – | 0.00 | 11 | 1.50 | – | 0.00 |
| DENv3 | 14 | 2.24 | – | 0.00 | 12 | 1.07 | – | 0.00 |
| DENv4 | 20 | 2.18 | – | 0.00 | 14 | 1.07 | – | 0.00 |
| DENv12 | 10 | 8.53 | 76 | 5.98 | 11 | 2.20 | 28 | 1.59 |
| DENv13 | 14 | 6.17 | 58 | 4.73 | 11 | 2.09 | 28 | 1.50 |
| DENv14 | 17 | 6.15 | 58 | 4.35 | 11 | 2.09 | 28 | 1.48 |
| DENv23 | 12 | 6.86 | 70 | 5.09 | 11 | 2.05 | 28 | 1.47 |
| DENv24 | 17 | 6.86 | 70 | 4.73 | 11 | 2.04 | 35 | 1.44 |
| DENv34 | 17 | 4.45 | 49 | 3.32 | 12 | 1.89 | 28 | 1.32 |
| DENv123 | 12 | 10.79 | 48 | 9.17 | 10 | 2.43 | 21 | 1.79 |
| DENv124 | 15 | 10.81 | 48 | 8.77 | 11 | 2.42 | 24 | 1.77 |
| DENv134 | 17 | 8.41 | 42 | 6.91 | 11 | 2.37 | 24 | 1.73 |
| DENv234 | 16 | 9.12 | 48 | 7.50 | 11 | 2.33 | 24 | 1.70 |
| DENv1234 | 14 | 13.05 | 38 | 11.31 | 9 | 2.58 | 19 | 1.91 |

very high risk at ages above 75 years is irrelevant due to the cut-off caused by modelling the human population with a step-death function. In addition the age-dependent biting rate that was derived from data results in a very low force of infection from relatively young ages (30 years) onwards so that the probability of an infection at higher ages is also very low which was not the case with a constant biting rate.

### Age-Dependent Vaccine Efficacy

Results when the risk of lethality is minimised and an age-dependent efficacy is assumed are presented in Table 5.10. Unsurprisingly, there is little difference between the optimal vaccination ages for the risk of lethality and those of hospitalisation. Again it can be seen that the optimal vaccination age decreases with an increasing number of serotypes particularly in CRS (b) and CRS (d). The results for a constant and an age-dependent efficacy with the aim of vaccinating being the reduction of lethality are also very similar. In fact most optimal vaccination ages are only slightly affected by the efficacy assumption and only very few (DENv12, DENv14 and DENv24 in CRS (b)) are significantly increased due

Table 5.10: The optimal vaccination age $A_1$ in months which minimises the lifetime expected risk $E$ of lethality for all CRSs. The vaccine efficacy is assumed serotype-specific and age-dependent as given in Table 1.1. '–' represents cases in which vaccination is not recommended, i.e. when $A_1$ was found to be above a reasonable age for humans.

| | CRS (a) | | CRS (b) | | CRS (c) | | CRS (d) | |
|---|---|---|---|---|---|---|---|---|
| | $A_1$ | $E_{\times 10^{-4}}$ | $A_1$ | $E_{\times 10^{-4}}$ | $A_1$ | $E_{\times 10^{-4}}$ | $A_1$ | $E_{\times 10^{-4}}$ |
| DENv1 | 11 | 4.66 | – | 0.00 | 12 | 2.76 | – | 0.00 |
| DENv2 | 9 | 5.39 | – | 0.00 | 14 | 2.83 | – | 0.00 |
| DENv3 | 14 | 3.09 | – | 0.00 | 14 | 2.07 | – | 0.00 |
| DENv4 | 20 | 4.41 | – | 0.00 | 15 | 2.65 | – | 0.00 |
| DENv12 | 10 | 10.06 | 108 | 6.28 | 11 | 4.27 | 42 | 2.78 |
| DENv13 | 14 | 7.75 | 63 | 5.47 | 11 | 4.14 | 38 | 2.75 |
| DENv14 | 17 | 9.10 | 108 | 5.75 | 12 | 4.29 | 38 | 2.81 |
| DENv23 | 12 | 8.50 | 73 | 5.78 | 12 | 4.05 | 42 | 2.66 |
| DENv24 | 17 | 9.87 | 108 | 5.37 | 13 | 4.21 | 42 | 2.72 |
| DENv34 | 17 | 7.52 | 63 | 5.15 | 14 | 4.07 | 38 | 2.68 |
| DENv123 | 12 | 13.16 | 48 | 10.67 | 11 | 4.70 | 28 | 3.27 |
| DENv124 | 14 | 14.55 | 51 | 11.40 | 11 | 4.75 | 28 | 3.30 |
| DENv134 | 15 | 12.21 | 43 | 9.72 | 11 | 4.72 | 28 | 3.30 |
| DENv234 | 15 | 12.97 | 49 | 10.27 | 11 | 4.67 | 28 | 3.25 |
| DENv1234 | 14 | 17.63 | 38 | 14.96 | 10 | 4.96 | 24 | 3.51 |

to the age-dependent efficacy. However, similarly to the risk of hospitalisation the lifetime expected risk is always higher with an age-dependent efficacy. This is caused by the fact that the optimal vaccination age tends to be very low, so that the pooled efficacy is higher than the age-dependent one at corresponding ages and therefore less infections will be prevented if the efficacy is indeed age-dependent. As for a constant efficacy, the most decisive factor for the optimal vaccination age is whether primary infections are risky or not.

**Licence Restrictions**

Almost all of the vaccination ages which lead to the greatest reduction in lifetime expected risk are below 9 years. Under the current licence restriction the ideal vaccination strategy can therefore not be applied. In Tables 5.11 and 5.12 the best time to vaccinate considering that Dengvaxia can only be used in in-

Table 5.11: The vaccination age $A_1$ in months which lies within the permitted age-range for the vaccine and minimises the lifetime expected risk $E$ of lethality. The percentage increase from the optimal lifetime expected risk $\delta_E\%$ is given for any case in which the optimal vaccination age lies outwith the permitted age-range of Dengvaxia. For cases in which vaccination is not recommended the minimal lifetime expected risk is zero, so that the percentage increase is given by $\infty$. The vaccine efficacy is assumed serotype-specific but age-independent as given in Table 1.1.

| | CRS (a) | | CRS (b) | | CRS (c) | | CRS (d) | |
|---|---|---|---|---|---|---|---|---|
| | $A_1$ | $\delta_E\%$ | $A_1$ | $\delta_E\%$ | $A_1$ | $\delta_E\%$ | $A_1$ | $\delta_E\%$ |
| DENv1 | 108 | 103 | 538 | $\infty$ | 108 | 410 | 538 | $\infty$ |
| DENv2 | 108 | 59 | 538 | $\infty$ | 108 | 344 | 538 | $\infty$ |
| DENv3 | 108 | 226 | 538 | $\infty$ | 108 | 558 | 538 | $\infty$ |
| DENv4 | 108 | 222 | 538 | $\infty$ | 108 | 539 | 538 | $\infty$ |
| DENv12 | 108 | 79 | 108 | 8 | 108 | 535 | 108 | 223 |
| DENv13 | 108 | 148 | 108 | 34 | 108 | 592 | 108 | 269 |
| DENv14 | 108 | 144 | 108 | 40 | 108 | 583 | 108 | 262 |
| DENv23 | 108 | 113 | 108 | 17 | 108 | 557 | 108 | 226 |
| DENv24 | 108 | 108 | 108 | 21 | 108 | 548 | 108 | 222 |
| DENv34 | 108 | 221 | 108 | 67 | 108 | 626 | 108 | 278 |
| DENv123 | 108 | 109 | 108 | 46 | 108 | 611 | 108 | 353 |
| DENv124 | 108 | 106 | 108 | 49 | 108 | 610 | 108 | 349 |
| DENv134 | 108 | 165 | 108 | 89 | 108 | 637 | 108 | 375 |
| DENv234 | 108 | 137 | 108 | 65 | 108 | 626 | 108 | 355 |
| DENv1234 | 108 | 127 | 108 | 80 | 108 | 620 | 108 | 390 |

Table 5.12: The vaccination age $A_1$ in months which lies within the permitted age-range for the vaccine and minimises the lifetime expected risk $E$ of lethality. The percentage increase from the optimal lifetime expected risk $\delta_E\%$ is given for any case in which the optimal vaccination age lies outwith the permitted age-range of Dengvaxia. For cases in which vaccination is not recommended the minimal lifetime expected risk is zero, so that the percentage increase is given by $\infty$. The vaccine efficacy is assumed serotype-specific and age-dependent as given in Table 1.1

| | CRS (a) | | CRS (b) | | CRS (c) | | CRS (d) | |
|---|---|---|---|---|---|---|---|---|
| | $A_1$ | $\delta_E\%$ | $A_1$ | $\delta_E\%$ | $A_1$ | $\delta_E\%$ | $A_1$ | $\delta_E\%$ |
| DENv1 | 108 | 70 | 538 | $\infty$ | 108 | 173 | 538 | $\infty$ |
| DENv2 | 108 | 33 | 538 | $\infty$ | 108 | 130 | 538 | $\infty$ |
| DENv3 | 108 | 134 | 538 | $\infty$ | 108 | 237 | 538 | $\infty$ |
| DENv4 | 108 | 52 | 538 | $\infty$ | 108 | 145 | 538 | $\infty$ |
| DENv12 | 108 | 50 | 108 | – | 108 | 222 | 108 | 79 |
| DENv13 | 108 | 95 | 108 | 14 | 108 | 246 | 108 | 97 |
| DENv14 | 108 | 60 | 108 | – | 108 | 224 | 108 | 80 |
| DENv23 | 108 | 69 | 108 | <1 | 108 | 226 | 108 | 74 |
| DENv24 | 108 | 40 | 108 | – | 108 | 205 | 108 | 60 |
| DENv34 | 108 | 85 | 108 | 2 | 108 | 229 | 108 | 76 |
| DENv123 | 108 | 69 | 108 | 23 | 108 | 265 | 108 | 144 |
| DENv124 | 108 | 50 | 108 | 10 | 108 | 258 | 108 | 136 |
| DENv134 | 108 | 79 | 108 | 29 | 108 | 266 | 108 | 143 |
| DENv234 | 108 | 62 | 108 | 16 | 108 | 258 | 108 | 131 |
| DENv1234 | 108 | 64 | 108 | 32 | 108 | 272 | 108 | 164 |

dividuals aged 9 to 45 years is shown respectively for a constant and an age-dependent efficacy. Due to the cut-off caused by the step-death function and the age-dependence of the biting rate there is very little discrepancy between the results for the risk of hospitalisation and that of lethality. It is therefore as expected that the restriction of the age has a similar effect for both risk functions. Vaccination to minimise the numbers of deaths caused by dengue should take place as close as possible to the optimal vaccination age, i.e. at 9 years if vaccination is recommended at younger ages and just before 45 years if it is not recommended. The percentage increase from the minimal lifetime expected risk depends on the CRS more than on other factors. It varies between 8% and over 637% for a constant efficacy and between less than 1% and 272% for an age-dependent efficacy if vaccination is recommended. The fact that the increase is lower in the case of an age-dependent efficacy is due to the increase in efficacy at 9 years. Independent of the efficacy CRS (c) is most affected by the age-restriction.

Without the restriction much better results can be achieved. It is important to remember that the restriction is based on the results from the Dengvaxia trials for the age-groups of children below 9 years and above 9 years [132]. However, the separation of trial participants into these age-groups is being challenged [38].

### 5.4.4 Summary for Endemic Regions with Four Serotypes

Similarly to the previous chapter the results for an endemic region with four serotypes will now be visualised in forest plots. The plots corresponding to a constant and an age-dependent vaccine efficacy are presented in Figures 5.13 and 5.14 respectively. Again the optimal vaccination ages as marked by the squares together with the age-intervals in which near-optimal vaccination is possible are shown for all four CRSs. Near-optimal vaccination is defined as vaccination which achieves a reduction of the lifetime expected risk which is at most 5% above the minimum. The minimal age for recipients according to the current licence is shown as well to make it easier to determine whether (near-)optimal vaccination would currently be possible in the considered scenarios. Note that for the scenarios considering a vaccine-induced risk the vaccine-induced negative effects are also assumed age-independent and age-dependent in the two plots respectively.

In Figure 5.13 it can clearly be seen that the optimal vaccination ages when no vaccine-induced risk is considered are much lower than if it is considered. In fact even the intervals in which near-optimal vaccination is possible are more limited in this case. Additionally in comparison to the previous chapter the results for hospitalisation and lethality are now very similar. In both cases they are very low and even if near-optimal vaccination is considered the current license does not permit vaccination in such a way that the lifetime expected risk can be reduced close to its minimum. In the case of vaccine-induced risk this is not the case. Under this assumption only CRS (a) leads to a near-optimal vaccination age-range which is completely below 9 years. The same observations are true in the age-dependent vaccine efficacy case (both with and without vaccine-induced risk) as can be seen from Figure 5.14. The age-dependence has only a small effect if a vaccine-induced risk is considered.

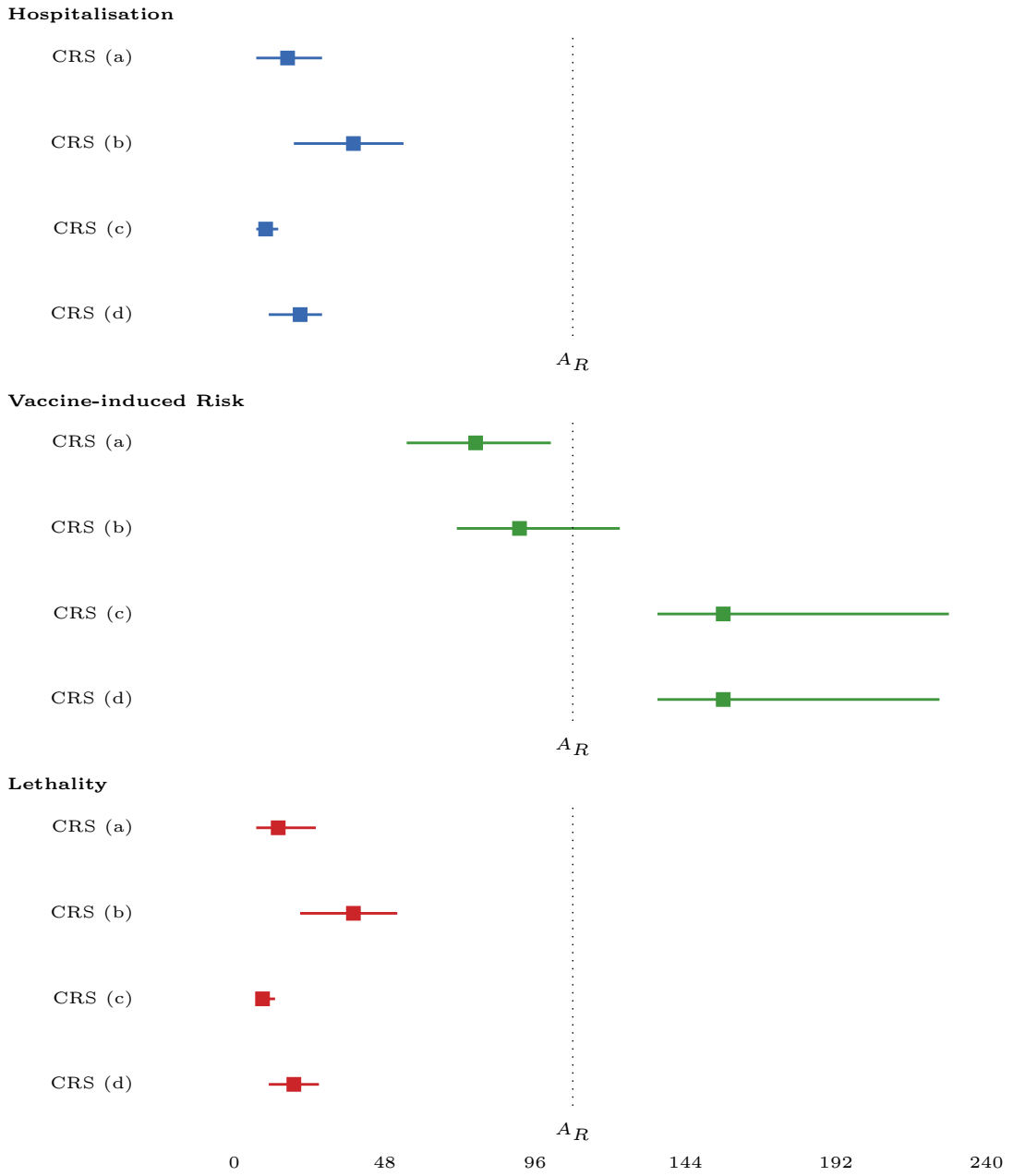



Figure 5.13: Forest plot for each scenario considering four coexisting serotypes with a constant vaccine efficacy. The squares mark the optimal vaccination age, while the horizontal lines indicate the interval in which the lifetime expected risk exceeds the minimum by no more than 5%. These intervals give an indication of the uncertainty in the optimal vaccination age. The vertical dotted line corresponds to the minimum age $A_R = 9$ years for vaccination according to current license restrictions.

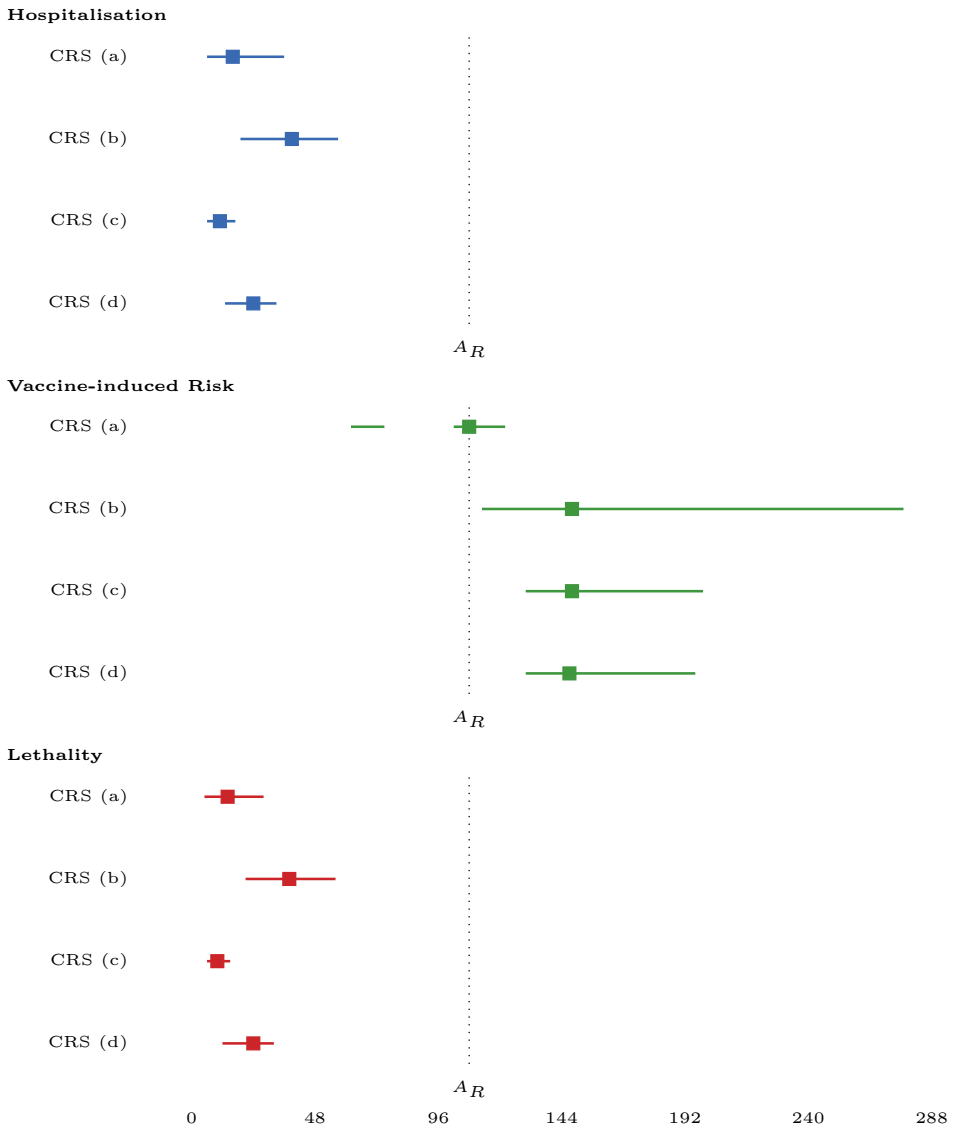



Figure 5.14: Forest plot for each scenario considering four coexisting serotypes with an age-dependent vaccine efficacy. The squares mark the optimal vaccination age, while the horizontal lines indicate the interval in which the lifetime expected risk exceeds the minimum by no more than 5%. These intervals give an indication of the uncertainty in the optimal vaccination age. For CRS (a) when a vaccine-induced risk is considered, two separate intervals in which the lifetime expected risk is at most 1.05 times as high as the minimum exist as shown by the discontinuous horizontal line. The vertical dotted line corresponds to the minimum age $A_R = 9$ years for vaccination according to current license restrictions.[1]

[1] In CRS (a) for a vaccine-induced risk the lifetime expected risk is close to its minimum in two distinct age intervals. The lifetime expected risk is first near optimal at around 70 months and increases again to above 1.05 times the optimum for some time. Once the first of the vaccination doses is, however, given with the higher efficacy it is near optimal again and reaches its optimum once all three doses are given with the higher efficacy, i.e. at 108 months.

An important conclusion that can be reached from the forest plots more easily than in the previous sections is that the optimal vaccination age is much more certain if PCI is considered. This was already hinted at in the discussion of the results since PCI corresponds to risk-free post-secondary infections. That means vaccination needs to take place before most secondary infections. In CRS (c) when primary infections are risky, it needs to take place before most primary infections occur as otherwise vaccination will be less effective. If there is no PCI, vaccination even after some primary, secondary or tertiary infections can still reduce the overall risk to some extent. Near-optimal vaccination is therefore possible in a wider range. If primary infections are considered to be risky the uncertainty is also smaller than otherwise as the largest effect will be obtained by vaccinating before primary infections.

Interestingly in the case of a vaccine-induced risk almost the exact opposite is the case, i.e. whether primary infections are risky or risk-free affects the uncertainty relatively little and PCI can lead sto a larger uncertainty in optimal vaccination age. Considering that vaccinating seronegatives can have a negative impact, vaccination in this case should be delayed until after the primary infection occurs. However, if post-secondary infections are risk-free the vaccine should be given exactly between the primary and secondary infection as otherwise it will have no effect. However, if the vaccine is given later there will be no additional risk in any recipients so that near-optimal vaccination can be carried out later. It needs to be kept in mind though, that a cost-benefit analysis could show that in this case the positive effect of vaccination does not outweigh the costs of the vaccination campaign. It can therefore be seen that especially in the case of a vaccine-induced risk more analysis from other perspectives is necessary before carrying out a vaccination campaign.

## 5.5 Conclusions

The results presented in this chapter were obtained for a single-serotype model as derived an analysed in Chapter 3. The age-dependent biting rate $q(a)$ was obtained from mosquito biting data. A step-death function was used to describe the population dynamics in Brazil in a more realistic way than in the previous chapter with a constant human death rate. The aim of vaccination was to reduce the risk of hospitalisation or of lethality. Based on an increased number of hospitalisations in some vaccine recipients during the vaccine trials the risk of

hospitalisation when vaccination has the potential to increase this risk was also considered. As there is still no agreement about whether the vaccine efficacy and vaccine-induced risk are age-dependent, serostatus-dependent or dependent on both factors to some extent the vaccine efficacy and vaccine-induced risk were initially assumed to be constant. However, subsequently the results using an age-dependent efficacy and serostatus- and age-dependent vaccine-induced risk were discussed.

The transmission model given in Equations (3.3) to (3.5) is a single-serotype model and does therefore not include any potential cross-reactions between the antibodies of different serotypes. This is true for naturally acquired antibodies as well as for antibodies due to successful vaccination. However, the lifetime expected risk in Equation (3.28) was defined in a way that permits different CRSs to be considered. Additionally, by defining the risk of an infection with serotype $i$ at age $a$ either based only on the infection history of an individual or on the infection and vaccination history of an individual, the different CRSs can be applied when antibodies due to infection and due to vaccination have the same effect or when antibodies due to vaccination may lead to a negative effect in some individuals. The potential cross-reactions that are generally accepted are ADE and PCI after two heterologous infections. ADE is often understood in such a way that a first natural infection is free of risk. Only once an individual with antibodies to one serotype is infected by another serotype are individuals at risk of complications [73, 87]. After two heterologous infections it is assumed that individuals can no longer get infected by the other serotypes, i.e. they are permanently immune to all four serotypes [53, 54, 115]. Both of these cross-reactions are only theorised and not fully understood so far. For this reason four CRSs were considered: all infections being risky, primary infections being risk-free, post-secondary infections being risk-free and only secondary infections being risky. In the model some serotype-specific parameters and functions were used to incorporate the differences between the four serotypes. This was done by assuming the vaccine efficacy and the decay of the maternal antibodies to be serotype-dependent and by determining serotype-specific effective reproduction numbers from case report data. These parameters and functions were then used to find the serotype-specific forces of infection and thus the lifetime expected risk for any number and combination of serotypes under the different assumptions relating to vaccine-induced risk for all CRSs. The optimal vaccination age was determined as the age at which the lifetime expected risk is minimal.

At younger ages the risk of hospitalisation and of lethality have very similar

shapes except for a slightly later peak of hospitalisations in children. The risk for lethality is always much lower than that of hospitalisation. Most lethal dengue cases will have been admitted to hospital at some point but not all hospitalisations have a fatal outcome so that this is to be expected. The age-dependent biting rate has an exponential term that cancels out the exponential term in the risk functions for hospitalisation and lethality in older individuals. In addition life expectancy in Brazil was taken as 73.8 years and incorporated through a step-death function. This resulted in a cut-off before the risk of lethality increases dramatically at older ages. Consequently very similar optimal vaccination ages were obtained for hospitalisation and lethality. Due to the slightly younger age at which children are most likely to die due to an infection some vaccination ages were a little lower for this risk. The lifetime expected risk is naturally lower for lethality than for hospitalisation. For the remainder of this section only the risk of hospitalisation will therefore be mentioned since all conclusions that can be drawn for the risk of hospitalisation are also true if lethality is considered.

The most relevant factor for the optimal vaccination age was found to be the considered CRS as can be surmised from Table 5.2. In CRS (a) the optimal vaccination ages are between 9 and 23 months which is very low. CRS (b) leads to higher vaccination ages between 38 and 76 months but vaccination is not recommended in every case, i.e. if there is only a single endemic serotype vaccination is counter-productive. For CRS (c) optimal vaccination ages between 10 and 17 months were found which are similar to those in CRS (a). CRS (d) resulted in optimal vaccination ages between 21 and 35 months but again vaccination is only recommended if at least two serotypes coexist. It can therefore be deduced that assuming risk-free primary infections increases the optimal vaccination age and that assuming risk-free post-secondary infections usually decreases it. The increase if primary-infections are risk-free is to be expected since in this case it is sufficient to vaccinate after a primary infection and vaccination can therefore be delayed until maternal antibodies decay. For risky primary infections there needs to be a balance between vaccinating too early, when children are still protected by maternal antibodies, and too late, when most primary infections will have already occurred. Risk-free post-secondary infections result in a lower optimal vaccination age since vaccination needs to take place before most secondary infections have occurred as otherwise it will not have any effect. This is less noticeable in CRS (c) when primary infections are risky as ideally these infections should already be prevented. In CRS (d) when only secondary infections are risky vaccination is ideal between the first and second natural infection.

Assuming an age-dependent efficacy has very little effect on any of these observations as can be seen from Table 5.3. The optimal vaccination ages are very similar overall and only significantly impacted in CRS (b). Even in this CRS the optimal vaccination age increases to 108 months only for combinations of two co-existing serotypes. The efficacy in children under 9 years of age is much lower if it is based on the age-groups from the Dengvaxia trials than if the data is pooled. A lower vaccine efficacy means that less infections can be prevented. Considering that the ideal time to vaccinate is almost always under 9 years of age independently of the efficacy assumption it is therefore not surprising that the minimal lifetime expected risk in the case of an age-dependent vaccine efficacy is higher.

Currently Dengvaxia is licensed for the use in individuals aged 9 to 45 years in Brazil. Almost all of the optimal vaccination ages are below 9 years and at the moment it is therefore not possible to apply the vaccine in the most effective way. However, vaccinating at 9 to 45 years can still be beneficial and as long as the restrictions are unchanged it is important to know what can be accomplished. The ages at which vaccination should be carried out are as close to the optimal vaccination age as possible, i.e. at 108 months (cf. Tables 5.4 and 5.5). For both efficacy assumptions, depending on the CRS, the lifetime expected risk is much higher than it would be if the vaccine could be used in younger children. In CRS (b) the impact of the restriction is least serious with up to 84% increase for a constant efficacy and no more than 29% for an age-dependent efficacy if vaccination is recommended. The highest increase can be observed for CRS (c) where the risk increases by more than 600% in some cases for a constant efficacy and by up to 276% for an age-dependent efficacy. The higher age-dependent efficacy for individuals above 9 years compared to the pooled efficacy is the reason why the age-restriction has a worse effect when the vaccine efficacy is constant. In endemic areas with a single serotype when primary infections are risk-free vaccination is not recommended but the negative impact of vaccination is smallest if vaccination is carried out as late as possible. This is true both for a constant and an age-dependent efficacy.

Recently some concern has been raised about the use of Dengvaxia in seronegative recipients. The WHO eventually changed their recommendation for the use of Dengvaxia and now advises that the vaccine only be used in seropositive individuals [133]. This is due to a higher proportion of hospitalisations in vaccine recipients that have not had a prior infection compared to unvaccinated seronegatives (cf. Table 1.2). Based on the corresponding data the lifetime expected risk of hospitalisation with a vaccine-induced risk was determined under the same

cross-reaction assumptions as for the risk of hospitalisation without a vaccine-induced risk. The optimal vaccination ages and minimal lifetime expected risk in this case are given in Tables 5.6 and 5.7 for a constant efficacy and constant vaccine-induced risk and an age-dependent efficacy and age-dependent vaccine-induced risk respectively. Incorporating this vaccine-induced risk has a huge effect. Vaccination ages are much higher particularly in CRS (c) and CRS (d) when post-secondary infections are assumed risk-free: between 156 and 311 months for a constant efficacy and between 147 and 407 months for an age-dependent efficacy. In CRS (a) and CRS (b) the optimal vaccination age is slightly lower between 77 and 258 months for a constant vaccine efficacy and between 108 and 323 months for an age-dependent efficacy. If there is only a single serotype in circulation vaccination with a constant efficacy is only recommended if this serotype is DENv3 or DENv4 and all infections are risky. This is due to the high risk of successfully vaccinating seronegatives against a non-endemic serotype thus increasing the risk associated with the natural infection. For DENv3 and DENv4 with all infections being risky the high efficacy means that this risk can be taken since some seronegatives will be successfully vaccinated against the endemic serotype. This becomes even clearer when considering an age-dependent efficacy for which vaccination is recommended if the primary infection is risky even if only a single serotype exists due to the higher efficacy at ages above 9 years compared to the pooled efficacy.

For several coexisting serotypes the optimal vaccination age in CRS (b) is higher than in CRS (a), but that in CRS (d) is almost identical to that in CRS (c). This is due to the fact that the vaccine-induced risk implies that it is often harmful to vaccinate seronegatives. Even if primary infections are risky many should have occurred before the vaccine is administered. In CRS (a) some primary infections can and should still be prevented in order to reduce the risk while in CRS (b) this is not the case due to primary infections being risk-free. In CRS (c) increasing the risk in seronegative recipients is not sensible since vaccinating seropositives successfully against any other serotype will result in the recipient no longer being at risk. This is also true in CRS (d) so that the optimal vaccination ages are almost the same. The optimal ages in CRS (c) and CRS (d) therefore correspond to the age at which most primary infections have occurred but at least some secondary infections can be prevented.

Considering an age-dependent rather than a constant efficacy and an age-dependent vaccine-induced risk results in similar optimal vaccination ages in CRS (c) and CRS (d) in general and a slight to moderate increase in optimal vaccination age in CRS (a) and CRS (b). However, when there is only a single serotype

in circulation and primary infections are risky the age-dependence has a large impact. Under this assumption vaccination is indeed recommended for any serotype which is not the case for the constant efficacy and constant vaccine-induced risk. Further the higher efficacy above 9 years compared to the pooled efficacy results in a lower lifetime expected risk whenever optimal vaccination ages are high. This is almost always the case when vaccination is recommended.

Most optimal vaccination ages obtained when the vaccine induces a risk in some recipients are within the permitted age-range for Dengvaxia in Brazil. For a constant vaccine efficacy when vaccination is recommended only combinations of three and four serotypes in CRS (a) and CRS (b) lead to optimal vaccination ages below 9 years. The vaccination ages that are ideal under the current restriction together with the percentage increase from the minimal lifetime expected risk are therefore shown in Table 5.8. The effect is rather small with increases between less than 1% and 7% when vaccination is recommended. However, if vaccination is carried out for a single endemic serotype even though it is not recommended the lifetime expected risk increases by as much as 82%. The licence restriction has no impact if two heterologous infections indeed confer PCI and vaccination is only carried out if it is recommended. However, under consideration of the vaccine-induced risk it is potentially best to vaccinate based on the serostatus rather than the age of a recipient. The licence restrictions may still need to be revised in light of this if it is determined that solely the serostatus is responsible for the increased risk and higher efficacy in individuals above the age of 9 years.

No vaccine-induced risk was considered for the risk of lethality due to no indication of a higher number of deaths so far. However, the risk of hospitalisation and of lethality are highly correlated with the number of deaths being much lower than the number of hospitalisations. The lack of data showing an increased risk of lethality due to vaccination of seronegatives might therefore be due to the relatively short time-frame and small trial cohort. Even though the results without a vaccine-induced risk were very similar for lethality and hospitalisation it will be necessary to determine the effect in the case of lethality once the relevant data becomes available.

As in the previous chapter a number of model assumptions were made in order to describe the transmission dynamics of dengue mathematically. However, any assumption needs to be considered carefully as it will have an impact of the results that the model yields.

The main difference to the model that was used in the previous chapter was the age-dependent biting rate which resulted in an age-dependent force of infection.

This assumption together with the assumption of a cut-off age caused by an assumed step-death function implies that the differences in the risk functions will most likely not be a key influence. A step-death function is certainly a much more realistic assumption for a country like Brazil than a constant death-rate. As discussed previously it is more realistic to assume some age-dependence in the transmission of dengue. However, the assumption is not straightforward as data is necessary to derive such an age-dependent rate. In Section 5.2 the limitations of the biting rate data which was used to obtain the biting rate for the model were already discussed. However, what was not discussed was the fact that the derived biting rate implicitly included the assumption that the force of infection is very low for adults. This is in fact a very strong assumption as it implies that mostly children can get infected with dengue. Therefore vaccinating after a certain age does not have any effect at all due to no subsequent infections taking place. Additionally the average age of infection is very low as only very few adults are infected. As a consequence the optimal vaccination ages for all scenarios were very low.

The low average age of infection is an important point to note, especially considering that the effective reproduction number, another key parameter of the model, was derived from data that showed that individuals of all ages are affected by dengue and which was averaged over Brazil. It is not unlikely that there are regions with a very low average age of infection. However, it is unlikely that these regions represent the average endemic region. It is therefore again important to keep in mind that the presented results only give an indication of the optimal vaccination age and cannot readily be applied to every endemic region equally or indeed to any specific endemic region without first determining the correct parameters and age-dependent functions for the target region of a vaccination campaign.

A completely new assumption in this chapter was the vaccine-induced risk. This is a very strong assumption which is based on a very small trial cohort. This needs to be kept in mind as it is possible that the vaccine-induced risk may indeed be very different from the one assumed here. In fact it is still argued whether the vaccine does indeed induce a risk at all. One possible argument for not making such an assumption is that it could be a short-term effect that was observed in the trial cohort. Consider the theory that the vaccine-induced risk is solely due to ADE and that seronegative vaccine recipients are only exposed to a risk similar to a natural secondary infection but may not experience any further infections. In this case it is possible that even seronegative recipients could benefit from

vaccination in the long-term. Considering the large effect this assumption has on the recommendations for vaccination campaigns any data that becomes available should be considered to refine the derived risk functions. This is particularly important in light of a much higher uncertainty in optimal vaccination age for a vaccine-induced risk as for the risk of hospitalisation without such an assumption.

The results in this chapter clearly reveal the need for more research into the effect of vaccine-induced antibodies. If vaccination causes a higher risk in seronegative recipients the optimal vaccination ages are highly impacted. For a single endemic serotype vaccination is often not even recommended with a vaccine-induced risk in any CRS if the efficacy and vaccine-induced risk are age-independent. Only if DENv3 or DENv4 is endemic in CRS (a) is vaccination beneficial. For several coexisting serotypes the optimal vaccination ages are much higher than if the vaccine-induced risk is not considered since vaccination of seronegatives can have adverse effects and should therefore be prevented.

The model was improved in comparison to the one used in the previous chapter. However, the results still only give an indication as to when the vaccine should be administered. They are more accurate since the human death rate was modelled by a step-death function and an age-dependent rate at which mosquitoes bite humans was used. The step-death rate is more realistic for a country like Brazil but results in a cut-off at the life expectancy so that the high risk in very old individuals is less relevant and may be slightly underestimated. On top of that the biting rate that was obtained from data starts to tend to zero at relatively young ages and therefore even further decreases the importance of the high risk at old ages. The force of infection is directly proportional to the biting rate and therefore age-dependent in the same way. This means that the probability of infection at older ages is very low. Dengue is generally considered a childhood disease but case report data shows that individuals of all ages contract it [29]. The biting rate data that was used in this model may be too crude to capture the actual dynamics accurately. However, it is difficult to obtain reliable biting data. The collection process is challenging as the number of bites will depend on the area and the habits of a specific individual. Additionally the number of bites is seasonal since the number of mosquitoes tends to be highest during summer and decreases in autumn and winter. Instead of using the biting rate data it may therefore be better to use serological data to obtain the force of infection. This will be done in the next chapter to further improve the accuracy of the results.

Chapter 6

# Optimal Vaccination Age using Seroprevalence Data

## 6.1 Introduction

Serological data is often used in epidemiological modelling to determine key parameters such as the force of infection and the basic reproduction number [44, 49, 56, 77, 78]. Muench [107] first introduced what he called the catalytic method to determine the force of infection from the age-dependent proportion of seropositives. This seminal work formed the basis for a number of more complex models that were developed in the following decades [49, 56, 77]. The advantage of using serological data as opposed to incidence data is their higher accuracy as serological surveys are not affected by underreporting or misdiagnosis. This is especially true if the data are obtained using serological tests with a high sensitivity and specificity. However, there are limitations when it comes to serological data as well. One of the main difficulties is that the proportion of seropositives will be affected by vaccination and estimates of the force of infection in a population where individuals have been vaccinated will be more difficult to obtain. Additionally, even without vaccination the presence of maternal antibodies at very young ages needs to be considered since the high proportion of seropositives at these ages will not correspond to a high force of infection.

In the previous chapter case report data and data recording the number of bites dependent on the age of the human were used to obtain the mosquito biting rate, the effective reproduction number and hence the force of infection for each of the four serotypes. However, dengue is a highly underreported disease for various reasons such as poor reporting mechanisms in some countries, asymptomatic infections and misdiagnosis due to symptoms being similar to other prevalent

diseases [22]. Additionally, it could be seen that the biting rate that was obtained resulted in a force of infection that tends to zero at fairly young ages (cf. Figure 5.1). This is not particularly realistic considering that case report data stratified by age shows that infections occur in all age-groups [29]. Using serological data to obtain the force of infection directly may therefore significantly increase the accuracy in the case of dengue. The force of infection can further be used to determine the mosquito biting rate more exactly than from biting data.

In this chapter the catalytic method will therefore be used to compute the force of infection and hence the mosquito biting rate from serological data. Considering serological data from the pre-vaccine era in Brazil means that the force of infection in the absence of vaccination can be determined. However, the presence of maternal antibodies at very young ages needs to be taken account of. No serotype-specific serological profile is available for Brazil so that case report data will still be used to ascertain serotype-specific forces of infection from the overall force of infection of dengue. These pre-vaccine serotype-specific forces of infection are then used to compute the serotype-specific force of infection for a particular vaccination strategy and thus the lifetime expected risk and optimal vaccination age.

Similarly to the previous chapter the risk of hospitalisation and lethality will be considered if vaccine-induced antibodies are assumed to have the same effect as naturally acquired ones both for a constant and an age-dependent efficacy. Based on a recently observed increased hospitalisation risk in some vaccine recipients a vaccine-induced risk is also considered for this risk function. As the use of the age-groups for children under 9 years and 9 years or older for the analysis of the Dengvaxia trial data is being criticised [38] and since it is believed that age is merely a surrogate for serostatus for some of the vaccination outcomes [4, 5, 75] the vaccine-induced risk in this chapter will be based on the pooled number of hospitalisations in the long-term follow-up of the trials as given in Table 1.2 (cf. Section 3.5) when the vaccine efficacy is assumed to be constant, i.e. the age-groups are being entirely disregarded in this case. All CRSs will be considered and whenever vaccination ages outwith the permitted age-range are determined to be optimal the age restriction is applied and the outcomes are compared.

## 6.2 Model Assumptions

The model given in Equations (3.3) to (3.5) is used in this chapter with a step-death function as introduced in the previous chapter by Equation (5.1). Additionally the biting rate is assumed to be age-dependent. However, instead of determining the biting rate from biting data and the force of infection from the effective reproduction number, the pre-vaccine force of infection will be determined directly from serological data.

In Section 3.2 the fractions of unaffected and infected humans of age $a$ at the steady-state were determined to be given by Equations (3.9) and (3.10) respectively. From these fractions the steady-state force of infection for a specific vaccination strategy can be computed by Equation (3.15). In order to use serological data from the pre-vaccine era to determine the force of infection for a specific vaccination strategy it is necessary to determine an expression for the force of infection before the introduction of the vaccine. This can be done by considering the steady-state fractions of unaffected and infected of age $a$ when there is no vaccination taking place, i.e.

$$u_0(a) = e^{-\int_0^a \lambda_0(s)C(s)ds}, \tag{6.1}$$

and

$$i_0(a) = e^{-\gamma_H a}\int_0^a \lambda_0(s)C(s)u_0(s)e^{\gamma_H s}\,\mathrm{d}s. \tag{6.2}$$

$\lambda_0(a)$ denotes the pre-vaccine force of infection in this case. It is obtained in a similar manner to Equation (3.15) and is given by

$$\lambda_0(a) = q(a)\frac{mbce^{-\mu_M\tau}}{\mu_M L}\frac{\int_0^\infty q(s)i_0(s)\pi_H(s)\,\mathrm{d}s}{1+\frac{c}{\mu_m L}\int_0^\infty q(s)i_0(s)\pi_H(s)\,\mathrm{d}s}. \tag{6.3}$$

By substituting Equation (6.3) into Equation (3.15) the steady-state force of infection for a specific vaccination strategy can therefore be expressed in terms of the pre-vaccine force of infection, i.e.

$$\lambda(a) = \lambda_0(a)\,\frac{\int_0^\infty q(s)i(s)\pi_H(s)\,\mathrm{d}s}{1+\frac{c}{\mu_m L}\int_0^\infty q(s)i(s)\pi_H(s)\,\mathrm{d}s}\,\frac{1+\frac{c}{\mu_m L}\int_0^\infty q(s)i_0(s)\pi_H(s)\,\mathrm{d}s}{\int_0^\infty q(s)i_0(s)\pi_H(s)\,\mathrm{d}s}. \tag{6.4}$$

It is not necessary to determine the effective reproduction numbers in this case since the pre-vaccine forces of infection for each of the serotypes are sufficient to calculate the force of infection for any vaccination age and thus the lifetime expected risk. In order to find the optimal vaccination age the serotype-specific forces of infection in the absence of vaccination need to be derived. This can be

achieved by considering serological data as has been shown, for example, by [49] for a number of different diseases. In the next section the catalytic method will therefore be applied to serotype-independent serological data that was collected during the pre-vaccine era in Brazil. It will be seen that it is still necessary to consider serotype-specific case report data to obtain the serotype-specific forces of infection from the overall pre-vaccine force of infection.

## 6.3 Force of Infection from Seroprevalence Data

Muench [107] first introduced the catalytic method to determine the force of infection of a disease from the serological profile of a population. Farrington [49] built on Muench's [107] model to describe the age-dependent force of infection by a more realistic function. In particular $s_0^+(a)$ the proportion of seropositives of age $a$ before the introduction of the vaccine is obtained by fitting the proportion of seropositives to the serological data. The age-dependent pre-vaccine force of infection can then be calculated according to the catalytic method, i.e.

$$\lambda_0(a) = \frac{\mathrm{d}s_0^+(a)}{\mathrm{d}a}\left(1 - s_0^+(a)\right)^{-1}. \tag{6.5}$$

Farrington [49] argues that a consistent age-dependent force of infection is non-negative for all ages but very low at birth due to maternal antibodies. One such consistent force of infection is obtained by setting the proportion of seropositives of age $a$ to

$$s_0^+(a) = 1 - e^{-\Lambda_0(a)} \tag{6.6}$$

with

$$\Lambda_0(a) = \int_0^a \lambda_0(s)\,\mathrm{d}s = k_3 a - \frac{k_1}{k_2} a e^{-k_2 a} - \frac{1}{k_2}\left(\frac{k_1}{k_2} - k_3\right)\left(e^{-k_2 a} - 1\right). \tag{6.7}$$

The catalytic method for this function results in the consistent pre-vaccine force of infection

$$\lambda_0(a) = (k_1 a - k_3)\, e^{-k_2 a} + k_3 \tag{6.8}$$

where $k_3$ is called the residual force of infection.

So far $s_0^+(a)$ does not take account of individuals who are protected by maternal antibodies so that if this function is fitted to serological data the effect

of maternal antibodies is ignored. Maternal antibodies decay quickly and will therefore only be detected in very young children. As long as the serological data does not record the proportion of seropositives for very young ages $s_0^+(a)$ can therefore be used to obtain the force of infection. However, if the serological data that is used records the fraction of seropositives even for young infants we need to distinguish between seropositivity due to maternal antibodies and due to a prior infection. This can be accomplished by considering individuals who are protected by maternal antibodies and susceptible individuals separately. Denote the age-density of individuals who are protected by maternal antibodies at age $a$ and at time $t$ by $M_H(a,t)$ and that for individuals who are susceptible by $S_H(a,t)$. Assuming a constant rate of decay of maternal antibodies $\delta$ the dynamics in the unaffected human population are then described by

$$\frac{\partial M_H}{\partial a} + \frac{\partial M_H}{\partial t} = -\delta M_H(a,t) - \mu_H(a) M_H(a,t), \tag{6.9}$$

and

$$\frac{\partial S_H}{\partial a} + \frac{\partial S_H}{\partial t} = \delta M_H(a,t) - (\lambda_H(a) + \mu_H(a))\, S_H(a,t) \tag{6.10}$$

with $M_H(0,t) = \frac{N_H}{L}$, $S_H(0,t) = 0$ for all $t \geq 0$ and $M_H(a,0) = M_{H,0}(a)$ and $S_H(a,0) = S_{H,0}(a)$ for all $a \geq 0$. The complete transmission model is thus given by Equations (3.3) to (3.5) where the equation for unaffected humans is replaced by Equations (6.9) and (6.10). At the steady-state when the fractions of individuals of age $a$ who are protected by maternal antibodies $m(a) = \frac{M_H(a)}{N_H(a)}$ and who are susceptible $s(a) = \frac{S_H(a)}{N_H(a)}$ are considered the above equations become

$$\frac{\mathrm{d}m}{\mathrm{d}a} = -\delta m(a),$$

and

$$\frac{\mathrm{d}s}{\mathrm{d}a} = \delta m(a) - \lambda(a) s(a),$$

with $m(0) = 1$ and $s(0) = 0$ where the subscript $H$ was dropped for convenience. In the absence of vaccination the fractions are therefore respectively obtained as

$$m_0(a) = e^{-\delta a}, \tag{6.11}$$

and

$$s_0(a) = e^{-\Lambda_0(a)} - e^{-\delta a} + \int_0^a \lambda_0(s) e^{-\delta s - (\Lambda_0(a) - \Lambda_0(s))s}\, \mathrm{d}. \tag{6.12}$$

Denote the steady-state proportion of all seropositives of age $a$ in the absence of vaccination by $\bar{s}_0^+(a)$. The only individuals who are seronegative at age $a$ are

those who are susceptible and therefore

$$\begin{aligned}\bar{s}_0^+(a) &= 1 - s_0(a), \\ &= 1 - e^{-\Lambda_0(a)} + e^{-\delta a} - \int_0^a \left((k_1 s - k_3)\, e^{-k_2 s} + k_3\right) e^{-\delta s - (\Lambda_0(a) - \Lambda_0(s))}\, \mathrm{d}s.\end{aligned} \tag{6.13}$$

Hence there are two possible methods to estimate the force of infection. The first is to take $\delta$ from the literature. Then $\bar{s}_0^+(a)$ can be fitted to serological data and the force of infection can be calculated according to Equation (6.8) ignoring the effect of maternal antibodies. However, since the available serological profile for dengue is serotype independent and most values for the decay of maternal antibodies in the literature are serotype-specific it is better to consider $\delta$ as an additional parameter that needs to be fitted.

Muench [107] assumed the force of infection to be constant, i.e. $\lambda_0(a) = k_3$. In the previous chapter the biting rate from mosquito biting data resulted in a force of infection of type $\lambda_0(a) = k_1 a e^{-k_2 a}$. This is another consistent force of infection and could also be considered. However, the best fit for the serological profile that was determined for Brazil before the introduction of the vaccine is obtained for a proportion of seropositives that results in the force of infection as given in Equation (6.8). This can be seen in Figure 6.1 where functions $\bar{s}_0^+(a)$ that result in each of these forces of infection are fitted to the data. Clearly an increasing number of parameters in general leads to a better fit. However, the goodness of fit statistics for the three fits indicate that $\bar{s}_0^+(a)$ as given in Equation (6.13) is the best choice.

The pre-vaccine steady-state force of infection for the presented serological profile is therefore obtained as

$$\lambda_0(a) = \left[(0.3086a - 0.0561)\, e^{-1.1441a} + 0.0561\right] \text{ year}^{-1} \tag{6.14}$$

where $\delta = 2.3350\,\text{year}^{-1}$ is the fitted decay of maternal antibodies resulting in an average duration of passive immunity of 0.4283 years.

The age-dependence of the force of infection is solely caused by that of the biting rate according to Equation (3.1). This means that the steady-state force of infection can be written as $\lambda_0(a) = \xi_T q(a)$ where $\xi_T$ is some constant. Similarly $\lambda_0^i(a) = \xi_i q(a)$ for $i = 1, 2, 3, 4$ where $\xi_i$ are serotype-specific constants. It is reasonable to assume that the biting behaviour of mosquitoes is neither influenced by which serotypes they are infected with nor by whether they are infected at

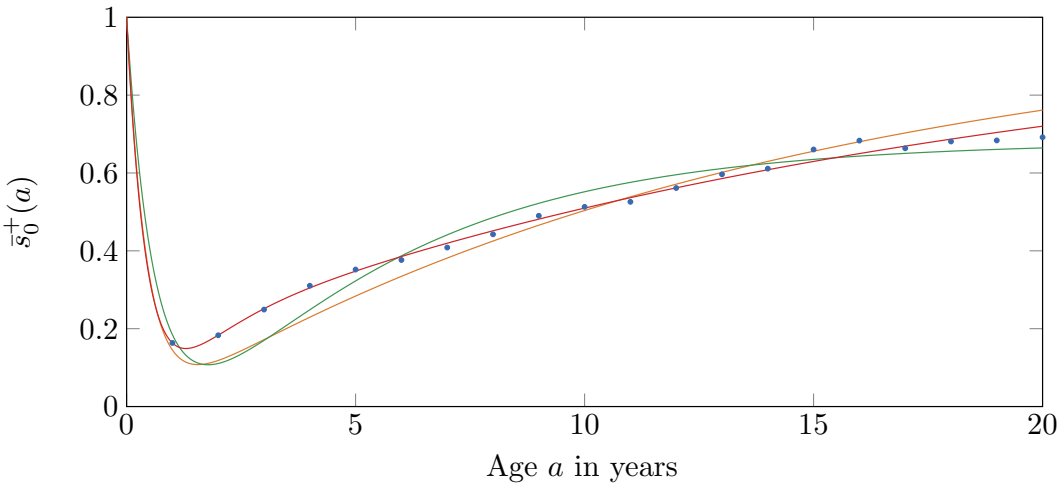



Figure 6.1: The blue dots show the age-dependent proportion of seropositives for individuals aged 1 to 20 years according to data that was collected before the introduction of Dengvaxia in Brazil [28]. Several different functions were fitted to this proportion. The catalytic method resulted in forces of infections given by $\lambda_0(a) = k_3$ (orange line), $\lambda_0(a) = k_1 a e^{-k_2 a}$ (green line) and $\lambda_0(a) = (k_1 a - k_3)\, e^{-k_2 a} + k_3$ (red line) respectively. The best fit is obtained by fitting Equation (6.13) as shown by the red line.

all and therefore the biting rate has to be serotype-independent. Further the cumulative force of infection of the four serotypes is the sum of the individual forces of infection. Consequently at the steady-state

$$\begin{aligned} \lambda_0(a) &= \lambda_0^1(a) + \lambda_0^2(a) + \lambda_0^3(a) + \lambda_0^4(a), \\ &= (\xi_1 + \xi_2 + \xi_3 + \xi_4)\, q(a), \\ &= \xi_T q(a), \end{aligned} \tag{6.15}$$

must hold where $\xi_i$ for $i = 1, 2, 3, 4$ are serotype-specific constants.

From serotype-specific serological data it would be possible to determine $\xi_i$ for each serotype. However, in the absence of such data the ratios $\xi_1 : \xi_2 : \xi_3 : \xi_4$ need to be determined in a different way. This can be done by considering case report data. In particular data collected through SINAN between 2000 and 2014 can be used to determine the number of reported cases for each serotype. The data shows that DENv2 caused the least infections during the recorded time while DENv1 caused the highest number of infections. It must be true that more infections caused by serotype $i$ imply a larger force of infection and therefore a larger $\xi_i$. From the model it is clear that seronegatives will become infected with serotype

$i$ at rate $\lambda_0^i(a)C_i(a)$ and if all four serotypes are circulating the probability that the individual is affected by serotype $i$ given that he or she is infected at age $a$ is therefore given by

$$\begin{aligned} p_i(a) &= \frac{\lambda_0^i(a)C_i(a)}{\lambda_0^1(a)C_1(a) + \lambda_0^2(a)C_2(a) + \lambda_0^3(a)C_3(a) + \lambda_0^4(a)C_4(a)}, \\ &\approx \frac{\lambda_0^i(a)C(a)}{\lambda_0^1(a)C(a) + \lambda_0^2(a)C(a) + \lambda_0^3(a)C(a) + \lambda_0^4(a)C(a)}, \\ &\approx \frac{\xi_i}{\xi_1 + \xi_2 + \xi_3 + \xi_4}, \end{aligned}$$

where $C_i(a) \approx C(a)$ for all four serotypes. This approximation is based on the fact that the rate of decay of maternal antibodies is similar for all serotypes at young ages and once maternal antibodies have declined (that is for most ages) $C_i(a) = 1$ for $i = 1, 2, 3, 4$ [119]. Considering that the age-dependence of the force of infection is assumed to be the same for all serotypes and that the decay of maternal antibodies is very similar $p_i(a)$ is (approximately) age-independent. It is therefore the probability of an infection being recorded as one of serotype $i$ and the ratios $\xi_1 : \xi_2 : \xi_3 : \xi_4$ can thus be taken from the ratios of the reported numbers of infections $n_1 : n_2 : n_3 : n_4$. Clearly this is only an approximation. While serotypes that have only recently been introduced to Brazil (i.e. DENv4) are under-represented at the beginning of the data this is balanced out by a higher number of reported cases of these serotypes for later years due to immunity against the remaining serotypes. If there is no ADE it can be argued that primary infections are most likely to be reported due to subsequent partial immunity. The case report data would then mainly correspond to primary infections and the above approximation would be fairly accurate. In fact, $q(a)$ and consequently $\lambda_0^i(a)$ $(i = 1, 2, 3, 4)$ are higher at young ages. At young ages secondary infections are less likely to have occurred and they are therefore less relevant. The estimates can therefore be used as a crude approximation even without considering secondary, tertiary and quaternary infections.

Using Equation (6.15) and considering the number of reported cases for each of the serotypes the serotype-specific forces of infection are computed as

$$\begin{aligned} \lambda_0^i(a) &= \frac{\xi_i}{\xi_1 + \xi_2 + \xi_3 + \xi_4}\lambda_0(a), \\ &\approx \frac{n_i}{n_1 + n_2 + n_3 + n_4}\lambda_0(a). \end{aligned} \tag{6.16}$$

Based on the SINAN data the forces of infection in the absence of vaccination are

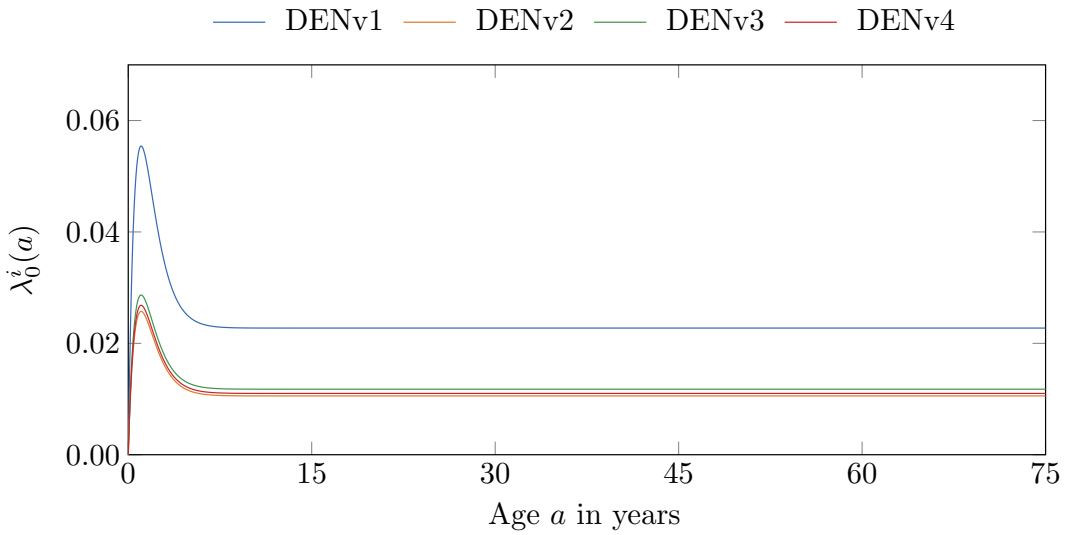



Figure 6.2: The serotype-specific forces of infection that were obtained from the serological profile (cf. Figure 6.1) and case report data before the introduction of a vaccine.

obtained as shown in Figure 6.2. Clearly the high number of reported DENv1 cases results in the highest force of infection. The remaining serotypes have very similar forces of infection. For all serotypes it is highest at young ages which is reasonable considering that dengue is a childhood disease.

$\xi_T$ can be determined from $\lambda_0(a)$ by substituting $q(a) = \frac{\lambda_0(a)}{\xi_T}$ into Equation (6.3) to obtain

$$1 = \frac{mbce^{-\mu_M \tau}}{\mu_M L} \frac{\int_0^\infty \lambda_0(a) i_0(a) \pi_H(a)\,\mathrm{d}a}{\xi_T \left(\xi_T + \frac{c}{\mu_M L} \int_0^\infty \lambda_0(a) i_0(a) \pi_H(a)\,\mathrm{d}a\right)}$$

which can be solved numerically to find the strictly positive solution $\xi_T$. Subsequently $q(a)$ can be computed as

$$q(a) = \left[(162.1207a - 29.4558)\, e^{-1.1441a} + 29.4558\right] \text{ year}^{-1}. \tag{6.17}$$

Having found the serotype-specific forces of infection in the absence of vaccination as well as the biting rate the force of infection for any serotype can be determined according to Equation (6.4) when vaccination takes place. As before the forces of infection for a specific vaccination strategy are necessary to determine the lifetime expected risk and thus the optimal vaccination age. The results obtained by doing so for the different risk assumptions and CRSs will be presented in the next section.

## 6.4 Optimal Vaccination Age

In the previous section serotype-specific forces of infection were derived from serological data and case report data that was collected before the introduction of Dengvaxia in Brazil. The best fit of the proportion of seropositives when maternal antibodies are considered was found to result in a force of infection with a residual term, i.e. for very high ages the force of infection tends to this residual force. Using data that records the number of mosquito bites for specific ages to obtain the mosquito biting rate and thus the force of infection as in the previous chapter did not lead to such a residual. Instead the force of infection that was derived from this data tended to zero fairly quickly. Dengue is typically considered a childhood disease so that this may seem reasonable. However, individuals of all ages get infected by the virus [29] and a residual force of infection at older ages is therefore more realistic.

In this section the serotype-specific forces of infection that were derived from serological data are used to compute the lifetime expected risk. In Section 6.4.1 the lifetime expected risk will be determined for the risk of hospitalisation when there is no distinction between vaccine-induced antibodies and natural infection, in Section 6.4.2 for the risk of hospitalisation when there is a vaccine-induced risk and in Section 6.4.3 for the risk of lethality. For each of these risk assumptions all CRSs will be considered. In addition to the theories regarding the interactions between the dengue virus serotypes there are a number of vaccine-related factors that are still being discussed. In particular it is unclear whether the vaccine efficacy is age-dependent or serostatus dependent. Similarly the increased risk when vaccine-induced risk is considered may solely depend on the serostatus or on the age of the recipient as well. Considering that the use of the age-groups for the analysis of the Dengvaxia trial is being challenged [38] the age-groups will be disregarded entirely to begin with, i.e. a constant efficacy will be assumed and in the case of vaccine-induced risk the pooled data is considered to determine the relative risks based on the infection and vaccination history of an individual as described in Section 3.5. However, the effect of the age-groups will briefly be discussed to highlight its effect. As before any number and combination of serotypes will be discussed in detail for the risk of hospitalisation when there is no distinction between vaccine-induced antibodies and natural infection and hospitalisation when there is a vaccine-induced risk. For each of these risk functions differences for the age-dependent efficacy case will be pointed out based on an area with a single endemic serotype. For the risk of lethality all results will be summarised. Lastly in each subsection the age-restriction of the current Dengvaxia licence for

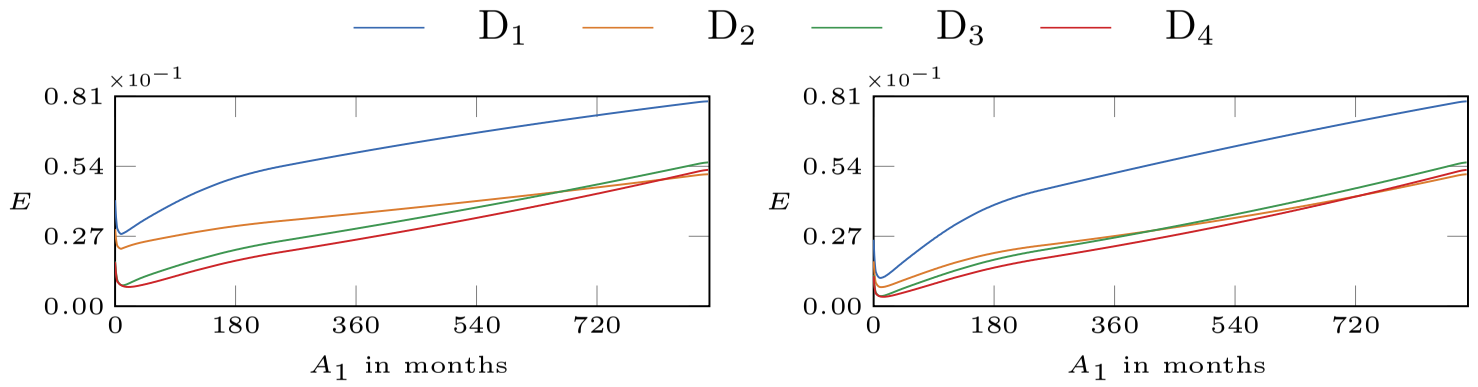
Brazil will be applied to all vaccination ages that are out with the range of 9 to 45 years.

### 6.4.1 Minimising the Risk of Hospitalisation

Reducing the risk of requiring hospital treatment due to an infection with dengue has the potential to significantly lower the socio-economic burden the disease causes in Brazil. In order to maximise the impact of vaccination it is necessary to determine the optimal age for individuals to be vaccinated. This will be done in this subsection when vaccine-induced antibodies are assumed to have the same effect as naturally acquired ones for all CRSs and any number and combination of serotypes. The efficacy of the vaccine will be assumed constant but the influence of an age-dependent efficacy will briefly be discussed. Initially vaccination will be permitted at any age that decreases the risk of hospitalisation to its minimum. However, since the use of Dengvaxia is restricted to individuals aged 9 to 45 years this constraint will be applied and the effect of it analysed.

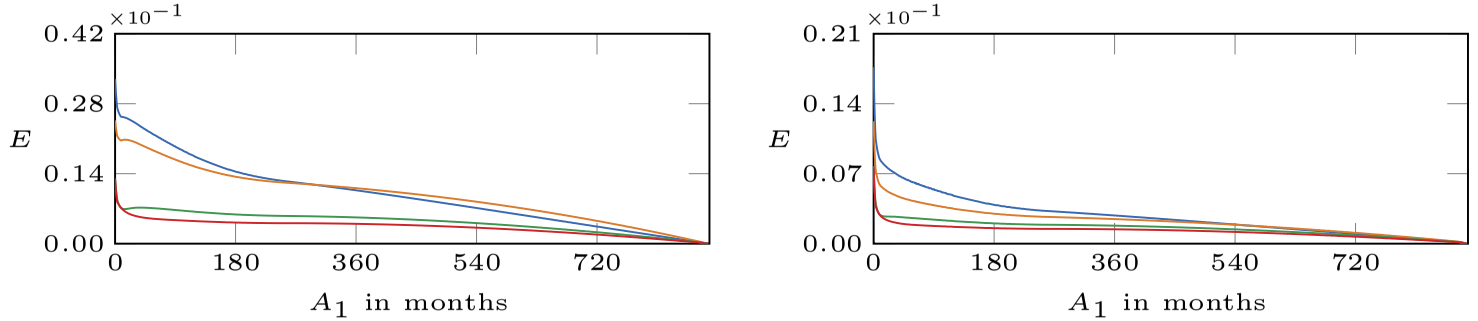
#### Constant Vaccine Efficacy

The lifetime expected risk as a function of the age at which the first vaccination dose is administered is shown in Figure 6.3 for an area with a single endemic serotype. The subfigures correspond to the four CRSs as described in Section 3.4. The non-zero residual force of infection clearly implies that infections occur at all ages. This can be seen from Figure 6.3a where all infections are assumed risky since the lifetime expected risk increases with age after the minimum is reached. This was not the case in the previous chapter where the force of infection for each serotype tended to zero very early and vaccination no longer had an effect later on. However, even with this residual force of infection the optimal vaccination age for a single endemic serotype is very low. This can be observed from Figure 6.3a. For DENv1, DENv2 and DENv3 the optimal vaccination age is only between 9 and 11 months, while for DENv4 it is 20 months. However, even though the optimal vaccination ages are similar the graph shows significant differences between the four serotypes. The differences are mainly caused by different forces of infection and the differences in vaccine efficacy. DENv1 has the highest force of infection, followed by DENv3, DENv4 and lastly DENv2. On the other hand the vaccine is most effective against DENv4 with almost 77% efficacy. It is similarly effective against DENv3 (72%), but less so against DENv1 and DENv2 with roughly 55% and 43% of vaccinated individuals being immunised successfully against these




(a) The optimal vaccination ages for DENv1, DENv2, DENv3 and DENv4 are 9, 9, 11 and 20 months respectively.

(c) The optimal vaccination ages for DENv1, DENv2, DENv3 and DENv4 are 11, 11, 11 and 14 months respectively.




(b) Vaccination is not recommended for any serotype.

(d) Vaccination is not recommended for any serotype.

Figure 6.3: The lifetime expected risk $E$ of hospitalisation in an endemic area where a single serotype exists as a function of age $A_1$ at which the first vaccine dose is administered. The vaccine efficacy is assumed serotype-specific but age-independent as given in Table 1.1. The subfigures (a)–(d) correspond to the CRS (a)–(d) respectively.

serotypes. From Figure 6.3a it is clear that in general for younger ages a higher efficacy results in a lower lifetime expected risk. However, by comparing DENv1 and DENv2 at young vaccination ages it is also apparent that the much higher force of infection of DENv1 is decisive if the efficacies are similar. For very high vaccination ages the lifetime expected risk caused by DENv2 is lower than that of DENv3 and DENv4. At these ages the force of infection seems to be decisive. In fact this can intuitively be explained; at young ages a higher efficacy will lead to many individuals that are successfully vaccinated against the endemic serotype so that the force of infection will be reduced and more natural infections will be prevented. Even if the force of infection in the absence of vaccination is higher than for other serotypes the risk may be lower. On the other hand, if vaccination takes place only later in life the higher force of infection in the absence of vaccination will have already caused many natural infections. Even with a higher vaccine efficacy not many infections can be prevented and therefore the lifetime expected risk in this case is lower for serotypes with a low force of infection. At very old vaccination ages, i.e. when the vaccine has hardly any effect since most infections will have occurred and individuals will die shortly after vaccination, the lifetime expected risk due to DENv2 is therefore lowest due to its low force of infection. The combination of a very high force of infection in the absence of vaccination and low efficacy for DENv1 leads to the highest risk independently of the vaccination age.

These observations are equally true in CRS (c). However, for asymptomatic third and fourth infections the optimal vaccination ages for DENv1 and DENv2 have slightly increased to 11 months, while that for DENv4 has decreased from 20 to 14 months in comparison to CRS (a). For all serotypes the lifetime expected risk is significantly lower and additionally the differences at young ages between the different serotypes are less pronounced. The reason for this is that the vaccination does not necessarily need to be effective against the serotype that is actually in circulation. In order to reduce the lifetime expected risk it is sufficient for the vaccine to be successful against two non-endemic serotypes before an infection with the one in existence occurs. Therefore even for serotypes with a lower efficacy the risk can be reduced due to the higher efficacy against the other serotypes. The higher risk due to DENv1 compared to the remaining serotypes is then caused by the higher force of infection.

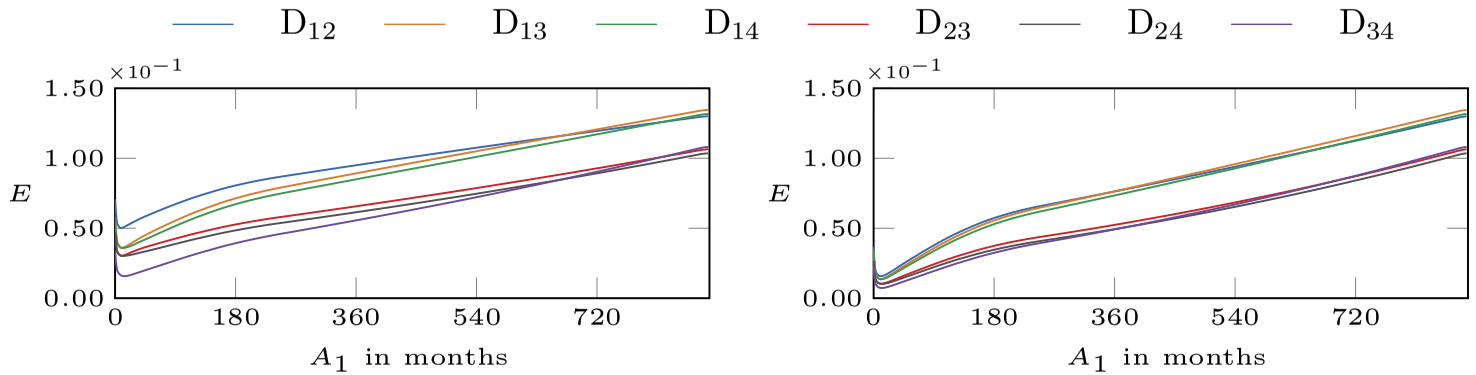
If primary infections are risk-free for a single serotype in existence as in Figures 6.3b and 6.3d vaccination is not recommended. The explanation for this is that the tetravalence of the vaccine makes it possible that an individual is immune

to a non-existent serotype before getting infected with the serotype in circulation. The natural infection is then a secondary, tertiary or quaternary infection and may be risky. Without vaccination it would have been risk-free and since there is no possibility of a secondary-type infection the lifetime expected risk without vaccination is zero. At younger ages DENv1 still poses the highest risk due to the high force of infection and relatively low efficacy, but at older ages DENv2 poses the highest risk even though it has a low force of infection in the absence of vaccination. This is because the vaccine is least effective against this serotype but quite effective against DENv3 and DENv4 so that there is a high probability of the infection with DENv2 occurring after successfully vaccinating against any of the other serotypes. In CRS (d) this effect is actually slightly less pronounced than in CRS (b) since the very low efficacy for DENv2 in comparison to DENv3 and DENv4 indicates that there is a good chance of successful immunisation against two of the other serotypes. An infection with DENv2 is therefore likely to be asymptomatic and will not contribute to the lifetime expected risk.

From considering an endemic area with a single serotype it can therefore be seen that the differences in force of infection and efficacy for the four serotypes are very relevant in determining the burden of dengue in an endemic region. However, the optimal vaccination age is very similar for all serotypes and more impacted by the CRS. Vaccination is counter-productive in CRS (b) and CRS (d) when primary infections are risk-free. Assuming risk-free post-secondary infections in CRS (c) results in optimal vaccination ages that are almost identical for all serotypes. In this case the differences in efficacy are less relevant since vaccination against non-endemic serotypes has the potential to reduce the risk caused by the endemic serotype.

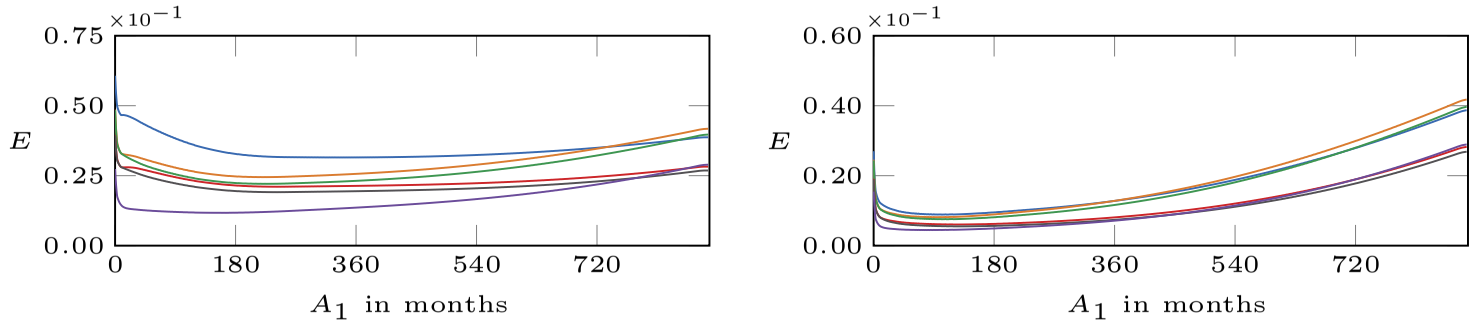
For an endemic region with two co-circulating serotypes the lifetime expected risk is presented in Figure 6.4. The lifetime expected risk in each CRS is higher for two circulating serotypes than for a single serotype. This is to be expected since an additional serotype will increase the number of risky infections.

Figure 6.4a shows the results for CRS (a). The optimal vaccination age for each combination is similarly low as the optimal vaccination age in an endemic region with only one serotype, i.e. between 9 and 14 months. It can further be seen that there are two groups of combinations which show a comparable behaviour of lifetime expected risk. Combinations including or not including DENv1 behave differently. Regions where DENv1 is endemic pose a higher lifetime expected risk than those where DENv1 is not present. This is caused by the very high force of infection in the absence of vaccination coupled with the low efficacy for DENv1 and




(a) The optimal vaccination ages for DENv12, DENv13, DENv14, DENv23, DENv24 and DENv34 are 9, 10, 11, 9, 11 and 14 months respectively.

(c) The optimal vaccination ages for DENv12, DENv13, DENv14, DENv23, DENv24 and DENv34 are 11, 11, 11, 11, 12 an 11 months respectively.




(b) The optimal vaccination ages for DENv12, DENv13, DENv14, DENv23, DENv24 and DENv34 are 335, 220, 223, 242, 242 and 165 months respectively.

(d) The optimal vaccination ages for DENv12, DENv13, DENv14, DENv23, DENv24 and DENv34 are 102, 102, 102, 119, 123 and 83 months respectively.

Figure 6.4: The lifetime expected risk $E$ of hospitalisation in an endemic area where two serotypes coexist as a function of age $A_1$ at which the first vaccine dose is administered. The vaccine efficacy is assumed serotype-specific but age-independent as given in Table 1.1. The subfigures (a)–(d) correspond to the CRS (a)–(d) respectively.

the higher number of infections that this entails. The effectiveness of the vaccine is indicative of how the lifetime expected risk of a combination compares to the remaining combinations since the forces of infection for the remaining serotypes are very similar, i.e. DENv12 results in the highest lifetime expected risk while DENv34 results in the lowest one for most vaccination ages. Again at very high ages this changes slightly with DENv13 causing the highest risk. The reasons for this are similar to the case of a single endemic serotype.

In CRS (b) vaccination is now recommended as can be seen from Figure 6.4b. The optimal vaccination age in this case is between 165 and 335 months, where the lowest vaccination age is obtained for the combination of DENv34. The reason for this increase in age compared to CRS (a) is that vaccination is now only necessary after a primary infection. In fact, since the vaccine may only be successful against one serotype, it is best to vaccinate after the first but before a second infection in order to reduce the lifetime expected risk most noticeably. Interestingly there is a wide age-range in which near optimal vaccination is possible. This is because vaccination is still beneficial even if it takes place after some secondary but before most tertiary or quaternary infections occur. The lifetime expected risk decreases in comparison to CRS (a) since the first infection no longer contributes to it. However, the effect of the different efficacies and forces of infection is analogous.

The results for CRS (c) are presented in Figure 6.4c where it can be seen that the optimal vaccination age is similar to that obtained in CRS (a), i.e. between 11 and 12 months. Similarly to the case of only one endemic serotype the asymptomaticity of post-secondary infections means that successful vaccination against any two serotypes is sufficient to reduce the risk. This results in the efficacy of the serotypes that are actually endemic being less relevant and therefore fewer differences between the two groups including and excluding DENv1. The difference between these two groups is solely caused by the high force of infection for DENv1.

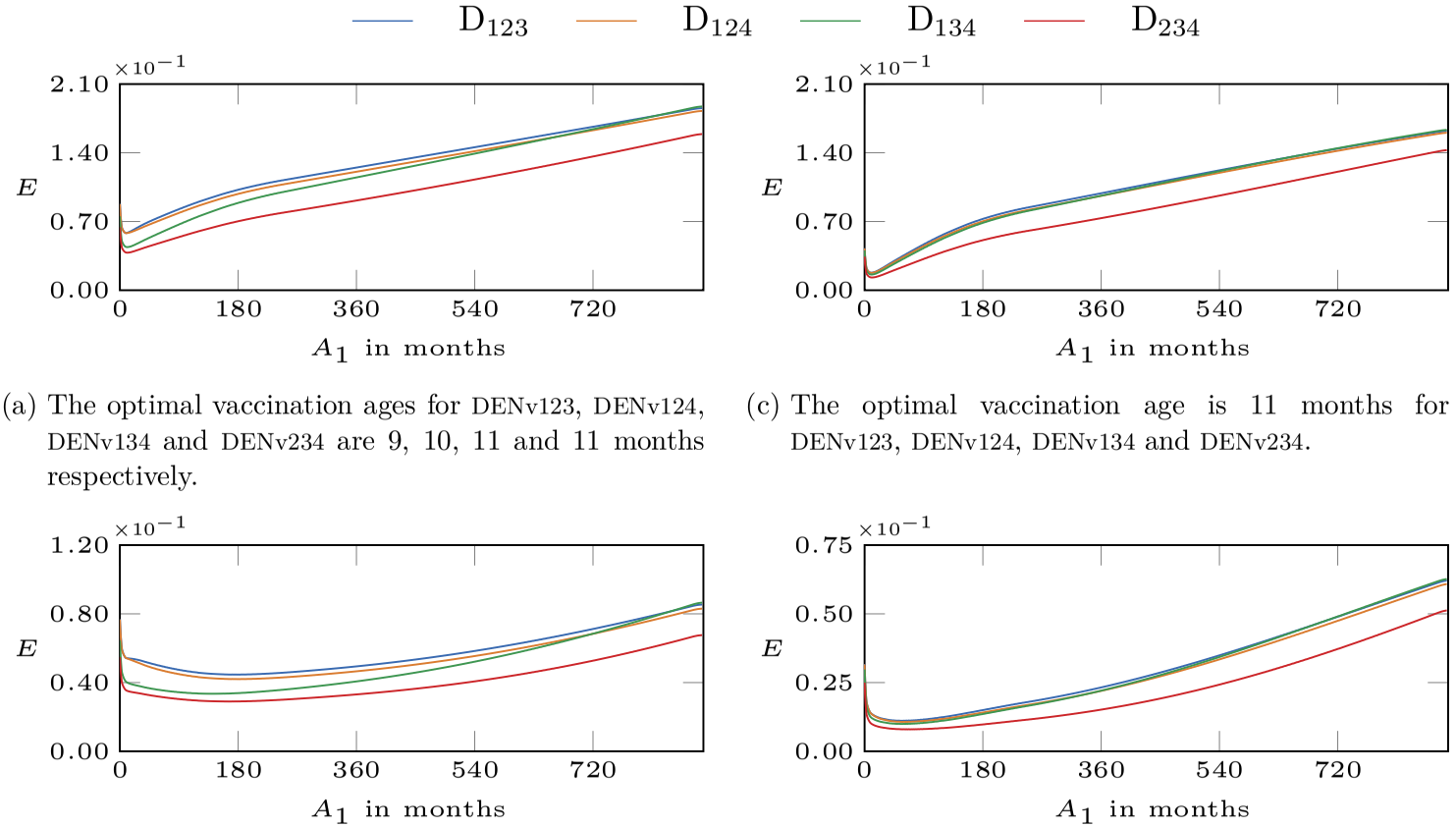
The observations that can be made in Figure 6.4d for CRS (d) are as expected after considering the remaining CRSs. In particular the optimal vaccination ages between 83 and 123 months are much higher than in CRS (c) since primary infections do not need to be targeted. However, they are lower than in CRS (b) and there is a much steeper increase after the optimal vaccination age since vaccination is only effective if it takes place before most secondary infections occur. In CRS (d) vaccination is ideally administered between the first and second infection when most secondary infections can be prevented. The high combined efficacy for DENv34 results in the lowest optimal age. This is because an earlier

age means that more infections can be prevented even if not all primary infections have occurred yet. Again the two groups of serotype combinations show a similar behaviour. In this case successful vaccination against any two serotypes before a primary infection or any serotype an individual was not infected with after a primary infection is sufficient for an individual to no longer be at risk.

For two coexisting serotypes the CRS is the most relevant factor when the optimal vaccination age is determined. CRS (a) and CRS (c) result in fairly similar vaccination ages since in both scenarios primary infections need to be targeted and therefore the ideal vaccination age is determined by the time at which a balance is found between vaccinating before most primary infections occur but after maternal antibodies have declined. CRS (b) results in much higher optimal vaccination ages since vaccination can reduce the risk if it is given after a primary infection but before a quaternary infection. The optimal vaccination age for CRS (d) is lower than in CRS (b) since vaccination is only beneficial if it takes place before an individual has had a secondary infection. The exact combination of serotypes is more relevant in CRS (b) and CRS (d) than in CRS (a) and CRS (c) since the optimal vaccination ages in the former vary much more. This is caused by the differences in force of infection and efficacy.

In endemic regions with three or four co-circulating serotypes the results are in fact very similar to those of two serotypes as can be seen in Figures 6.5 and 6.6 respectively. The optimal vaccination ages in CRS (a) and CRS (c) are very low between 9 and 11 months in all cases of three coexisting serotypes and is 11 months for all four serotypes coexisting. In CRS (b) the vaccination age increases to between 140 and 182 months for three coexisting serotypes and to 124 months for all four serotypes in an endemic region. Similarly to two coexisting serotypes the age again decreases in CRS (d) where it is between 56 and 63 months and 48 months for three and four endemic serotypes respectively. Note that these optimal vaccination ages are in general lower than the corresponding ones for two endemic serotypes. This is to be expected as a higher number of serotypes decreases the average age of infection. The targeted infections occur earlier and therefore the vaccine needs to be administered earlier if more serotypes coexist. From Figure 6.5 it can also be seen that the higher force of infection for DENv1 means that combinations of three serotypes that include DENv1 result in a higher lifetime expected risk.

The optimal vaccination age if the aim is to reduce the risk of hospitalisation mostly depends on the considered CRS. If primary infections are considered risky,



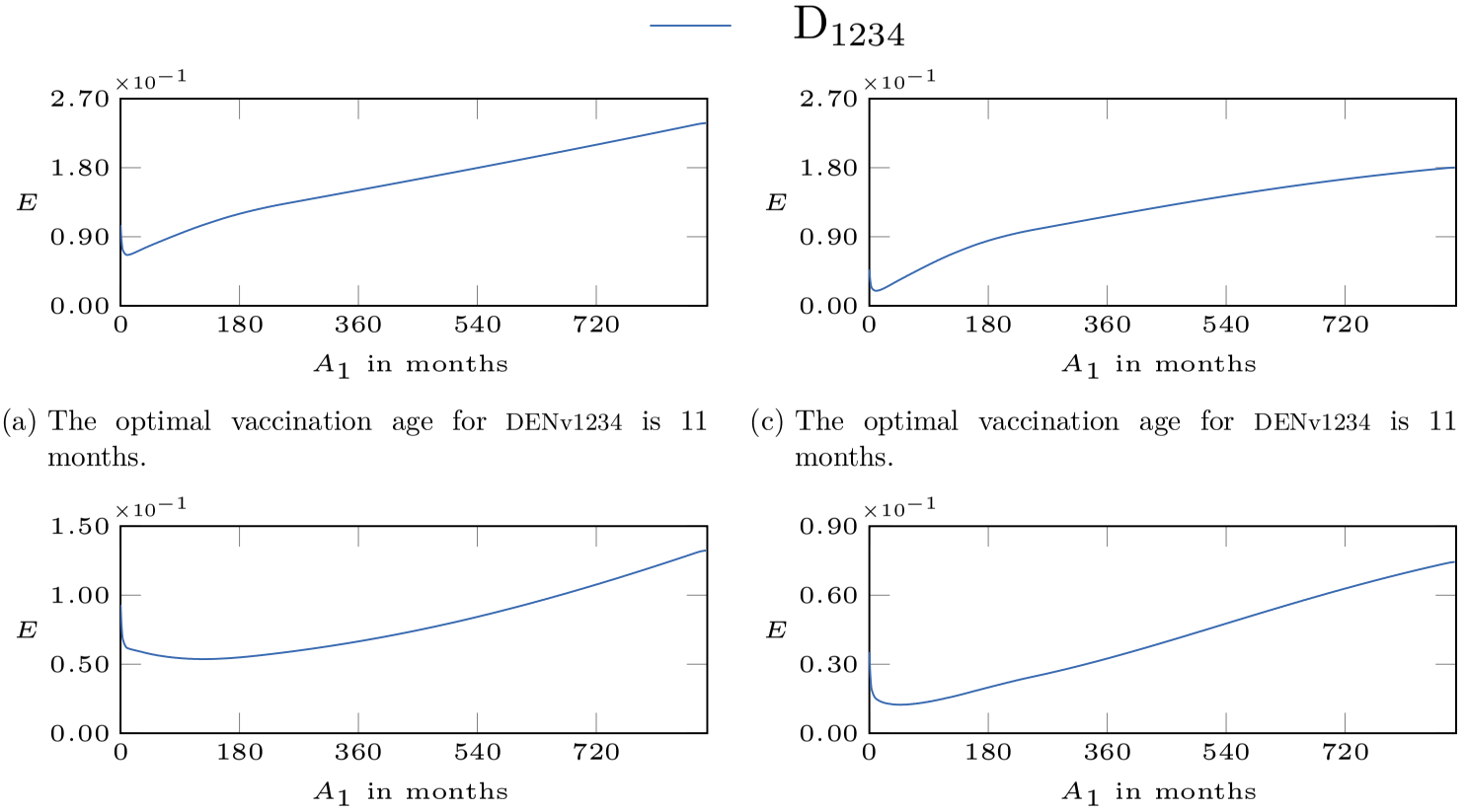

(a) The optimal vaccination ages for DENv123, DENv124, DENv134 and DENv234 are 9, 10, 11 and 11 months respectively.

(c) The optimal vaccination age is 11 months for DENv123, DENv124, DENv134 and DENv234.

(b) The optimal vaccination ages for DENv123, DENv124, DENv134 and DENv234 are 182, 182, 140 and 165 months respectively.

(d) The optimal vaccination ages for DENv123, DENv124, DENv134 and DENv234 are 56, 63, 56 and 63 months respectively.

Figure 6.5: The lifetime expected risk $E$ of hospitalisation in an endemic area where three serotypes coexist as a function of age $A_1$ at which the first vaccine dose is administered. The vaccine efficacy is assumed serotype-specific but age-independent as given in Table 1.1. The subfigures (a)–(d) correspond to the CRS (a)–(d) respectively.




(a) The optimal vaccination age for DENv1234 is 11 months.

(b) The optimal vaccination age for DENv1234 is 124 months.

(c) The optimal vaccination age for DENv1234 is 11 months.

(d) The optimal vaccination age for DENv1234 is 48 months.

Figure 6.6: The lifetime expected risk $E$ of hospitalisation in an endemic area where all four serotypes coexist as a function of age $A_1$ at which the first vaccine dose is administered. The vaccine efficacy is assumed serotype-specific but age-independent as given in Table 1.1. The subfigures (a)–(d) correspond to the CRS (a)–(d) respectively.

i.e. in CRS (a) and CRS (c), the optimal vaccination age for a constant vaccine efficacy is between 9 and 20 months for all combinations of serotypes. It does not vary significantly with the assumption of PCI since the first infection in this case accounts for a significant part of the risk. On the other hand, in CRS (c) and CRS (d) the optimal age is much higher, but now depends significantly on whether third and fourth infections are asymptomatic and also varies slightly with the number of serotypes. In general the optimal age decreases with the number of serotypes, particularly in CRS (c) and CRS (d).

All results for a constant efficacy when the risk of hospitalisation is being minimised through vaccination are summarised in Table 6.1. From the results it is clear that considering risky primary infections (CRS (a) and CRS (c)) leads to a very low optimal vaccination age independently of the number or combination of serotypes. The optimal vaccination age lies between 9 and 14 months for almost all serotype combinations in both scenarios, The only exception is CRS (a) when the only serotype in circulation is DENv4 in which case the first dose should be administered to children aged 20 months. However, assuming risk-free primary infections as in CRS (b) and CRS (d) result in very different optimal vaccination ages. All optimal vaccination ages significantly increase with the exception of those for a single serotype in circulation. For regions with a single endemic serotype vaccination is in fact not recommended at all since primary infections are risk-free and Dengvaxia is an imperfect vaccine. Vaccination leads to an increased risk in this case since it can result in immunity to a non-existing serotype prior to natural infection with the endemic serotype so that the otherwise harmless natural infection is similar to a secondary infection and therefore risky. In CRS (d) optimal vaccination ages do not increase as much as in CRS (b). This is caused by the fact that vaccination in this case is only beneficial if it is given before a secondary infection takes place. Vaccination can still reduce the risk in CRS (b) even after a secondary infection so that the age is higher. Interestingly the optimal vaccination ages significantly vary with the number of coexisting serotypes if primary infections are considered risk-free but there is much less variation if they are considered risky. In CRS (b) and CRS (d) more co-existing serotypes lead to a lower optimal vaccination age. This is plausible since a higher number of serotypes decreases the average ages of infection. This decrease in age is not relevant in CRS (a) and CRS (c) since vaccination already takes place as soon as maternal antibodies decline sufficiently in order to prevent as many primary infections as possible. However, in CRS (b) and CRS (d) the decrease in average age of the second infection leads to a lower optimal vaccination age which is particularly

Table 6.1: The optimal vaccination age $A_1$ in months which minimises the lifetime expected risk $E$ of hospitalisation for all CRSs. The vaccine efficacy is assumed serotype-specific but age-independent as given in Table 1.1. '–' represents cases in which vaccination is not recommended, i.e. when $A_1$ was found to be above a reasonable age for humans.

| | CRS (a) | | CRS (b) | | CRS (c) | | CRS (d) | |
|---|---|---|---|---|---|---|---|---|
| | $A_1$ | $E_{\times 10^{-3}}$ | $A_1$ | $E_{\times 10^{-3}}$ | $A_1$ | $E_{\times 10^{-3}}$ | $A_1$ | $E_{\times 10^{-3}}$ |
| DENv1 | 9 | 27.89 | – | 0.00 | 11 | 10.94 | – | 0.00 |
| DENv2 | 9 | 22.17 | – | 0.00 | 11 | 7.37 | – | 0.00 |
| DENv3 | 11 | 8.07 | – | 0.00 | 11 | 3.90 | – | 0.00 |
| DENv4 | 20 | 7.43 | – | 0.00 | 14 | 3.64 | – | 0.00 |
| DENv12 | 9 | 50.06 | 335 | 31.51 | 11 | 15.73 | 102 | 8.86 |
| DENv13 | 10 | 36.04 | 220 | 24.48 | 11 | 13.71 | 102 | 8.11 |
| DENv14 | 11 | 35.86 | 223 | 22.09 | 11 | 13.52 | 102 | 7.54 |
| DENv23 | 9 | 30.36 | 242 | 21.04 | 11 | 10.41 | 119 | 6.04 |
| DENv24 | 11 | 30.19 | 242 | 19.10 | 12 | 10.23 | 123 | 5.51 |
| DENv34 | 14 | 15.75 | 165 | 11.72 | 11 | 7.31 | 83 | 4.45 |
| DENv123 | 9 | 58.24 | 182 | 44.64 | 11 | 17.83 | 56 | 11.07 |
| DENv124 | 10 | 58.17 | 182 | 42.00 | 11 | 17.67 | 63 | 10.68 |
| DENv134 | 11 | 43.92 | 140 | 33.50 | 11 | 15.96 | 56 | 9.93 |
| DENv234 | 11 | 38.26 | 165 | 28.98 | 11 | 12.97 | 63 | 7.98 |
| DENv1234 | 11 | 66.27 | 124 | 53.67 | 11 | 19.53 | 48 | 12.37 |

clear in CRS (d) since then vaccination is most beneficial if it takes place between the primary and secondary infection. On the other hand the minimal lifetime expected risk is lowest if only a single serotype circulates and additional serotypes lead to an increase in lifetime expected risk as one would expect independently of the CRSs.

### Age-Dependent Vaccine Efficacy

For an age-dependent efficacy the results are summarised in Table 6.2. Most of the observations are similar to those for a constant efficacy. However, in CRS (a) and CRS (c) there are some serotype combinations that lead to much higher vaccination ages than in the case of a constant efficacy and the minimal lifetime expected risk is higher in all cases independent of whether the optimal vaccination age is affected by the assumption of an age-dependent efficacy. The increase in minimal lifetime expected risk for cases where the optimal vaccination age is unchanged in comparison to a constant efficacy is due to the fact that the age-dependent efficacy at these young ages is lower than if the efficacy is pooled. For those cases where the optimal vaccination age increases to 108 months (i.e.

9 years) the vaccine efficacy is actually higher than if it is assumed constant. However, in these cases the efficacy at young ages is much lower so that it is more effective to allow some infections to take place at young ages and instead vaccinate as soon as the higher efficacy applies. That these early infections occur can be seen since the lifetime expected risk is higher in comparison to the constant efficacy case, i.e. even though the vaccine efficacy is higher the risk is higher since less infections can be prevented. In CRS (c) and CRS (d) it is crucial for the vaccination to take place before a secondary infection. There is no longer any trade-off effect in allowing more break-through cases to occur in order for the vaccine to be more effective if these break-through cases are secondary infections. Therefore the optimal vaccination age is less influenced than in CRS (a).

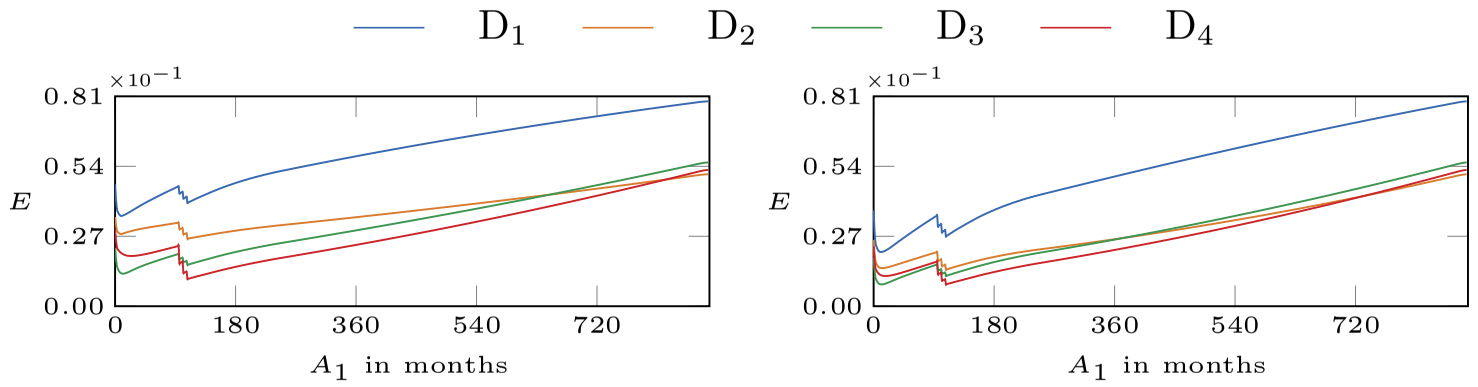
In CRS (b) and CRS (d) there is much less dramatic difference between the optimal vaccination ages for a constant and an age-dependent efficacy. CRS (d) requires vaccination at slightly higher ages if vaccination was recommended before 9 years for constant efficacy. For some combinations in CRS (b) and CRS (d) which already led to vaccination above 9 years the optimal vaccination age actually decreases slightly, e.g. in an endemic area with DENv14 or DENv24. In all scenarios

Table 6.2: The optimal vaccination age $A_1$ in months which minimises the lifetime expected risk $E$ of hospitalisation for all CRSs. The vaccine efficacy is assumed serotype-specific and age-dependent as given in Table 1.1. '–' represents cases in which vaccination is not recommended, i.e. when $A_1$ was found to be above a reasonable age for humans.

| | CRS (a) | | CRS (b) | | CRS (c) | | CRS (d) | |
|---|---|---|---|---|---|---|---|---|
| | $A_1$ | $E_{\times 10^{-3}}$ | $A_1$ | $E_{\times 10^{-3}}$ | $A_1$ | $E_{\times 10^{-3}}$ | $A_1$ | $E_{\times 10^{-3}}$ |
| DENv1 | 9 | 34.83 | – | 0.00 | 11 | 2.09 | – | 0.00 |
| DENv2 | 108 | 26.04 | – | 0.00 | 108 | 1.41 | – | 0.00 |
| DENv3 | 11 | 12.57 | – | 0.00 | 11 | 0.84 | – | 0.00 |
| DENv4 | 108 | 10.49 | – | 0.00 | 108 | 0.84 | – | 0.00 |
| DENv12 | 9 | 62.67 | 253 | 29.38 | 11 | 30.83 | 109 | 7.06 |
| DENv13 | 10 | 47.50 | 212 | 22.88 | 11 | 27.36 | 109 | 6.50 |
| DENv14 | 108 | 50.34 | 213 | 19.45 | 12 | 29.24 | 109 | 5.78 |
| DENv23 | 10 | 40.55 | 242 | 19.56 | 11 | 21.47 | 109 | 4.71 |
| DENv24 | 108 | 36.54 | 236 | 16.68 | 108 | 22.08 | 109 | 4.06 |
| DENv34 | 108 | 26.44 | 133 | 9.84 | 14 | 19.08 | 109 | 3.33 |
| DENv123 | 9 | 75.41 | 165 | 41.33 | 11 | 35.43 | 109 | 9.93 |
| DENv124 | 108 | 76.41 | 167 | 37.61 | 11 | 36.70 | 109 | 9.20 |
| DENv134 | 108 | 66.28 | 130 | 29.75 | 11 | 34.15 | 109 | 8.66 |
| DENv234 | 108 | 52.48 | 165 | 25.64 | 14 | 29.21 | 109 | 6.43 |
| DENv1234 | 108 | 92.32 | 119 | 4.81 | 11 | 40.27 | 108 | 12.21 |

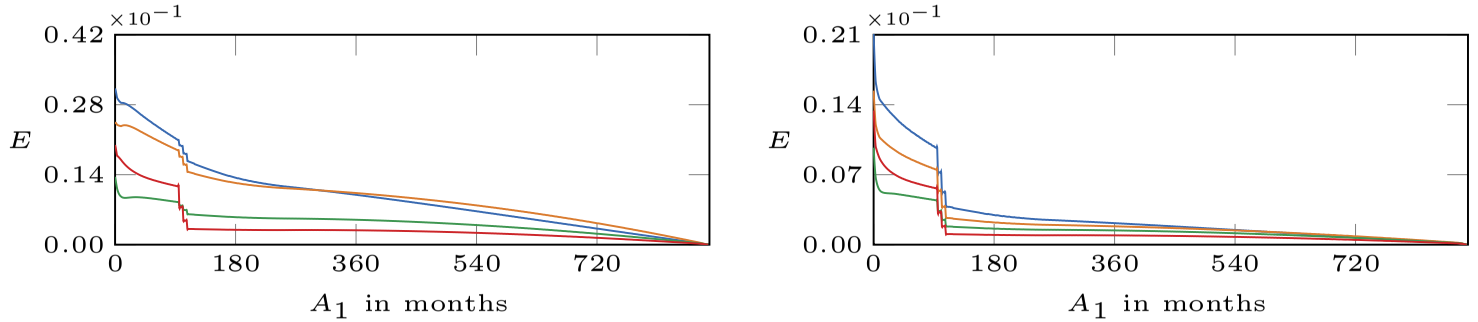
the minimal lifetime expected risk is lower than in the case of a constant efficacy since the vaccine is more effective at the ages at which vaccination takes place if age-dependence is assumed.

The lifetime expected risk for an endemic region with a single serotype when the efficacy is assumed age-dependent is shown in Figure 6.7. By comparing these results to those for a constant efficacy in Figure 6.3 the effect of the age-dependent efficacy can be seen. While the main observations are equivalent there are three features that distinguish the two assumptions regarding efficacy independent of the considered CRSs. The vaccine efficacy is lower for children under the age of 9 and higher for children aged 9 and above for each of the serotypes when compared to the pooled efficacy. This leads to the most noticeable difference being that there are three drops in the lifetime expected risk. These drops are caused by one of the three vaccination doses being administered above the age of 9 years so that the vaccine efficacy increases. The last drop corresponds to the vaccination age of the first dose being 9 years when all three doses are administered with the higher efficacy. Since the vaccine efficacy is least affected by the age for DENv3 the drops are least pronounced for this serotype and similarly since the difference is most significant for DENv4 the lifetime expected risk is most affected. The second difference is that the lifetime expected risk is higher at younger ages and once the higher efficacy applies it is lower for some time than in the constant efficacy case. Again this is due to the efficacy being lower for children under the age of 9 in comparison to the constant efficacy and higher otherwise. Once vaccination takes place at very high ages there is no longer any difference since no infections will be prevented. Since in the younger age-range the efficacy for DENv3 in the age-dependent case is higher than that of DENv4, DENv4 poses a higher risk than DENv3 at younger ages. Lastly in CRS (b) and CRS (d) vaccination is still not recommended at all. However CRS (a) and CRS (c) result in an increase in the optimal vaccination age to 108 months for DENv2 and DENv4. This is due to the significant increase in efficacy for those two serotypes if vaccination is administered at 9 years or above so that it is better to allow some break-through cases to occur if more infections can be prevented due to the much higher efficacy. The lifetime expected risk and optimal vaccination ages for several coexisting serotypes are similarly affected by the assumption of an age-dependent vaccine efficacy as can be seen from Table 6.2 and will therefore not be discussed in any more detail.




(a) The optimal vaccination ages for DENv1, DENv2, DENv3 and DENv4 are 9, 108, 11 and 108 months respectively.

(c) The optimal vaccination ages for DENv1, DENv2, DENv3 and DENv4 are 11, 108, 11 and 108 months respectively.




(b) Vaccination is not recommended for any serotype.

(d) Vaccination is not recommended for any serotype.

Figure 6.7: The lifetime expected risk $E$ of hospitalisation in an endemic area where a single serotype exists as a function of age $A_1$ at which the first vaccine dose is administered. The vaccine efficacy is assumed serotype-specific and age-dependent as given in Table 1.1. The subfigures (a)–(d) correspond to the CRS (a)–(d) respectively.

### Licence Restrictions

Many of the optimal vaccination ages that minimise the risk of hospitalisation are far below 9 years which is the minimum age for Dengvaxia recipients. Particularly low ages were found for CRS (a) and CRS (c). However, even for CRS (d) some optimal vaccination ages are below 9 years. The assumption of an age-dependent efficacy leads to more cases with an optimal vaccination age that is in accordance with the licence restrictions of Dengvaxia. The question therefore remains at which age the vaccine should be given considering that it is only permitted to vaccinate individuals between the ages of 9 and 45 years and how this influences the lifetime expected risk.

In Tables 6.3 and 6.4 the recommended vaccination ages for individuals aged 9 to 45 years are given together with the percentage increase of the lifetime expected risk from its minimum for a constant vaccine efficacy and an age-dependent

Table 6.3: The vaccination age $A_1$ in months which lies within the permitted age-range for the vaccine and minimises the lifetime expected risk $E$ of hospitalisation. The percentage increase from the optimal lifetime expected risk $\delta_E\%$ is given for any case in which the optimal vaccination age lies outwith the permitted age-range of Dengvaxia. For cases in which vaccination is not recommended the minimal lifetime expected risk is zero, so that the percentage increase is given by $\infty$. The vaccine efficacy is assumed serotype-specific but age-independent as given in Table 1.1.

| | CRS (a) | | CRS (b) | | CRS (c) | | CRS (d) | |
|---|---|---|---|---|---|---|---|---|
| | $A_1$ | $\delta_E\%$ | $A_1$ | $\delta_E\%$ | $A_1$ | $\delta_E\%$ | $A_1$ | $\delta_E\%$ |
| DENv1 | 108 | 52 | 538 | $\infty$ | 108 | 167 | 538 | $\infty$ |
| DENv2 | 108 | 26 | 538 | $\infty$ | 108 | 113 | 538 | $\infty$ |
| DENv3 | 108 | 108 | 538 | $\infty$ | 108 | 223 | 538 | $\infty$ |
| DENv4 | 108 | 73 | 538 | $\infty$ | 108 | 175 | 538 | $\infty$ |
| DENv12 | 108 | 41 | 335 | – | 108 | 170 | 109 | $< 1$ |
| DENv13 | 108 | 64 | 220 | – | 108 | 194 | 109 | $< 1$ |
| DENv14 | 108 | 54 | 223 | – | 108 | 182 | 109 | $< 1$ |
| DENv23 | 108 | 48 | 242 | – | 108 | 162 | 119 | – |
| DENv24 | 108 | 36 | 242 | – | 108 | 145 | 123 | – |
| DENv34 | 108 | 89 | 165 | – | 108 | 205 | 109 | 1 |
| DENv123 | 108 | 50 | 182 | – | 108 | 196 | 109 | 9 |
| DENv124 | 108 | 43 | 182 | – | 108 | 188 | 109 | 7 |
| DENv134 | 108 | 64 | 140 | – | 108 | 207 | 109 | 9 |
| DENv234 | 108 | 51 | 165 | – | 108 | 179 | 109 | 4 |
| DENv1234 | 108 | 51 | 124 | – | 108 | 212 | 108 | 19 |

Table 6.4: The vaccination age $A_1$ in months which lies within the permitted age-range for the vaccine and minimises the lifetime expected risk $E$ of hospitalisation. The percentage increase from the optimal lifetime expected risk $\delta_E\%$ is given for any case in which the optimal vaccination age lies outwith the permitted age-range of Dengvaxia. For cases in which vaccination is not recommended the minimal lifetime expected risk is zero, so that the percentage increase is given by $\infty$. The vaccine efficacy is assumed serotype-specific and age-dependent as given in Table 1.1

| | CRS (a) | | CRS (b) | | CRS (c) | | CRS (d) | |
|---|---|---|---|---|---|---|---|---|
| | $A_1$ | $\delta_E\%$ | $A_1$ | $\delta_E\%$ | $A_1$ | $\delta_E\%$ | $A_1$ | $\delta_E\%$ |
| DENv1 | 108 | 14 | 538 | $\infty$ | 108 | 29 | 538 | $\infty$ |
| DENv2 | 108 | – | 538 | $\infty$ | 108 | – | 538 | $\infty$ |
| DENv3 | 108 | 27 | 538 | $\infty$ | 108 | 38 | 538 | $\infty$ |
| DENv4 | 108 | – | 538 | $\infty$ | 108 | – | 538 | $\infty$ |
| DENv12 | 108 | 5 | 253 | – | 108 | 27 | 109 | – |
| DENv13 | 108 | 17 | 212 | – | 108 | 37 | 109 | – |
| DENv14 | 108 | – | 213 | – | 108 | 19 | 109 | – |
| DENv23 | 108 | 4 | 242 | – | 108 | 16 | 109 | – |
| DENv24 | 108 | – | 236 | – | 108 | – | 109 | – |
| DENv34 | 108 | – | 133 | – | 108 | 4 | 109 | – |
| DENv123 | 108 | 9 | 165 | – | 108 | 39 | 109 | – |
| DENv124 | 108 | – | 167 | – | 108 | 27 | 109 | – |
| DENv134 | 108 | – | 130 | – | 108 | 32 | 109 | – |
| DENv234 | 108 | – | 165 | – | 108 | 12 | 109 | – |
| DENv1234 | 108 | – | 119 | – | 108 | 40 | 108 | – |

one respectively. It can be seen that for all combinations of serotypes with an optimal vaccination age below 9 years the vaccination should take place as soon as possible once it is permitted, i.e. at 9 years (108 months). The lifetime expected risk, however, can increase significantly from its minimum particularly for a constant efficacy. It is in fact more than twice the minimal one for some serotype combinations in this case. For an age-dependent efficacy the increase is not quite as drastic (only up to 40% increase) due to the higher efficacy for children above the age of 9 years. In general the lifetime expected risk increases more in CRS (a) and CRS (c) than in CRS (b) and CRS (d). In fact, whenever vaccination is recommended in CRS (b) the optimal vaccination age already adheres to the licence restriction so that there is no negative effect in this scenario. In regions with a single endemic serotype vaccination is not recommended if primary infections are risk-free. However, if vaccination is given it should be done as late as possible, i.e. at 45 years.

The effect of the licence restriction in the case of serotype-specific forces of infection being derived from serological data and case report data is therefore very similar to the previous model. The restriction is only sensible, or has no effect, if CRS (b) realistically describes the cross-reactions of the different serotypes. If other cross-reactions influence the risk of an infection, restricting the vaccination age to the range of 9 to 45 years makes it difficult to deploy the vaccine in the most effective way. It is therefore crucial to determine which CRS is most realistic. Depending on the actual CRS it might be necessary to revise the minimal age for vaccination.

### 6.4.2 Minimising the Risk of Hospitalisation under Consideration of Vaccine-Induced Risk

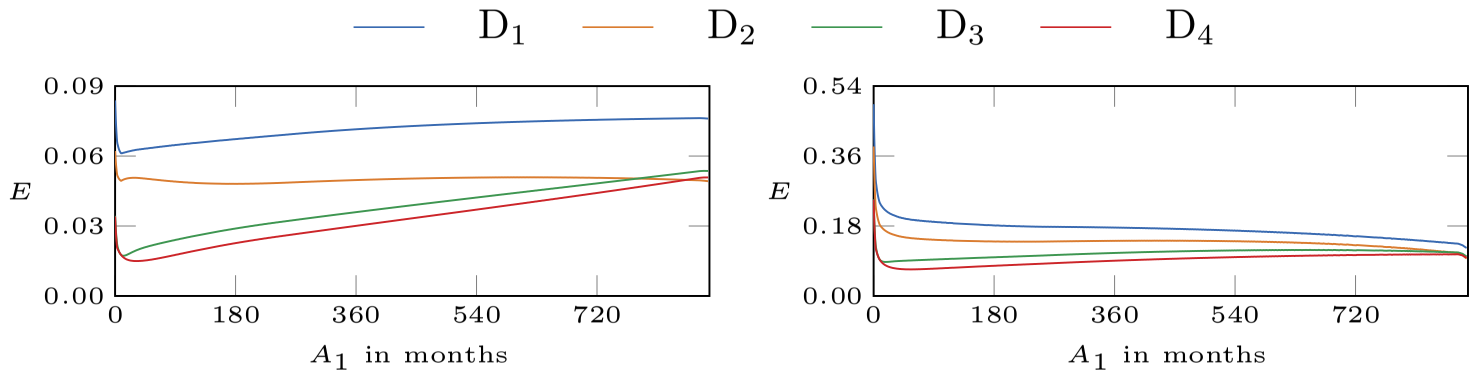
One of the biggest challenges of dengue vaccination is the possibility for vaccine-induced ADE. For Dengvaxia initial safety analysis did not indicate such a vaccine-induced risk. However, in the long-term follow-up of the trials an increased number of hospitalisations in seronegative recipients was observed compared to the seronegative control group (cf. Table 1.2). In light of these recent findings it is important to determine the optimal vaccination age when vaccination has potentially negative effects. In fact, it may be possible that vaccination is not recommended at all due to the increased risk in some recipients.

In this subsection a vaccine-induced risk based on the recorded number of hospitalisations in the long-term follow-up will be considered. Initially the age-groups that were used for the analysis of the trial data will be entirely disregarded, i.e. both the vaccine efficacy and the induced risk will be assumed constant based on the pooled data given in Tables 1.1 and 1.2. However, the results obtained using the age-dependent data will briefly be compared. Lastly the current age-restriction of Dengvaxia will be applied and the consequences of this restriction discussed.

#### Constant Vaccine Efficacy and Vaccine-Induced Risk

To begin with consider a region with a single endemic serotype. The results for such a region are shown in Figure 6.8 where as before the subfigures correspond to the four CRSs. Clearly the vaccine-induced risk has a very large impact on the lifetime expected risk. This can be seen by comparing Figures 6.3 and 6.8.

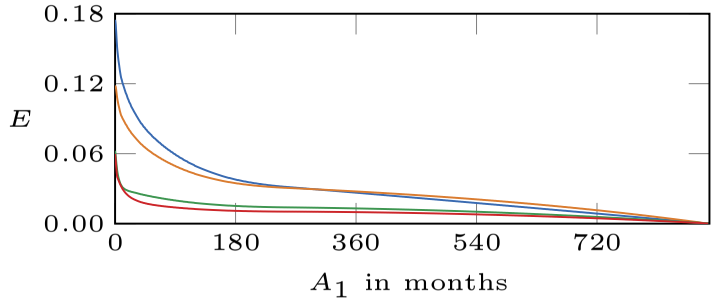
When all infections are risky as shown in Figure 6.8a the vaccination age is between 9 and 32 months for DENv1, DENv3 and DENv4 which is very low. For



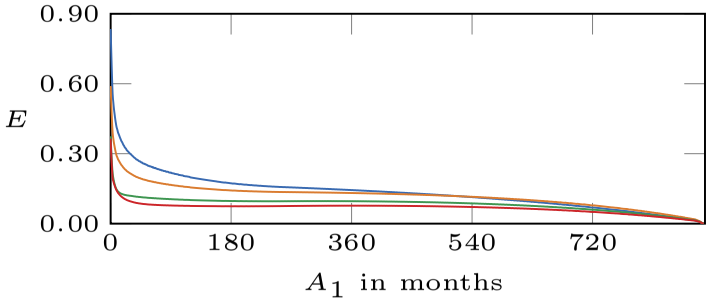

(a) The optimal vaccination ages for DENv1, DENv2, DENv3 and DENv4 are 9, 182, 12 and 32 months respectively.




(c) Vaccination is not recommended for DENv1 and DENv2. The optimal vaccination ages for DENv3 and DENv4 are 17 and 56 months respectively.




(b) Vaccination is not recommended for any serotype.




(d) Vaccination is not recommended for any serotype.

Figure 6.8: The lifetime expected risk $E$ of hospitalisation in an endemic area where a single serotype exists as a function of age $A_1$ at which the first vaccine dose is administered. The vaccine efficacy is assumed serotype-specific but age-independent as given in Table 1.1. An age-independent vaccine-induced risk is considered as given in Table 1.2. The subfigures (a)–(d) correspond to the CRS (a)–(d) respectively.

DENv2 the optimal vaccination age is 182 months and therefore much higher. Interestingly it can be seen that for DENv2 vaccination has very little effect independently of the vaccination age. The lifetime expected risk is a rather flat function of the age at which the first dose of Dengvaxia is administered. For the remaining serotypes the impact of vaccination is larger, particularly for DENv3 and DENv4. This is most likely due to how effectively the vaccine immunises against each of the serotypes. The efficacy is highest for DENv4, followed by DENv3 and DENv1 and lowest for DENv2. It can therefore be expected that few infections caused by DENv2 can be prevented. Successful vaccination causes a higher risk in seronegative recipients and with the vaccine being more effective against DENv1, DENv3 and DENv4 the likelihood is high that if only DENv2 is endemic and vaccination takes place early many seronegative individuals will be successfully vaccinated against non-endemic serotypes. In this case some DENv2 infections may be prevented but the vaccine will induce a higher risk in many post-vaccination infections. It is therefore better to vaccinate later so as to prevent successful vaccination of seronegatives against non-endemic serotypes. However, vaccinating later means that fewer infections caused by DENv2 can be prevented. Therefore the lifetime expected risk cannot be significantly reduced independently of the vaccination age. For the remaining serotypes most infections can be prevented if vaccination takes place early. With the higher efficacy for these serotypes it is more likely that the vaccine will be effective against the endemic serotypes. However, in order to reduce the number of successfully vaccinated seronegatives vaccination takes place at ages at which some maternal antibodies persist. The lower the efficacy the more relevant it is to reduce the chances of successful immunisation of seronegatives so that for DENv1 the optimal vaccination age is lowest. The decay of maternal antibodies protecting against DENv4 is slower compared to that of DENv3 and therefore the optimal vaccination ages vary even though the efficacy against those two serotypes is similar.

From Figure 6.8a one can further see that the highest risk is due to DENv1 followed by DENv2, DENv3 and finally DENv4 for most vaccination ages. At very high vaccination ages the risk due to DENv2 is in fact lower than that of DENv3 and DENv4. Considering that the force of infection for DENv1 is highest and that it is very similar for the remaining serotypes this is not surprising. The low efficacy for DENv2 results in vaccination having very little effect, while the high efficacy for DENv3 and DENv4 means that the risk can significantly be reduced.

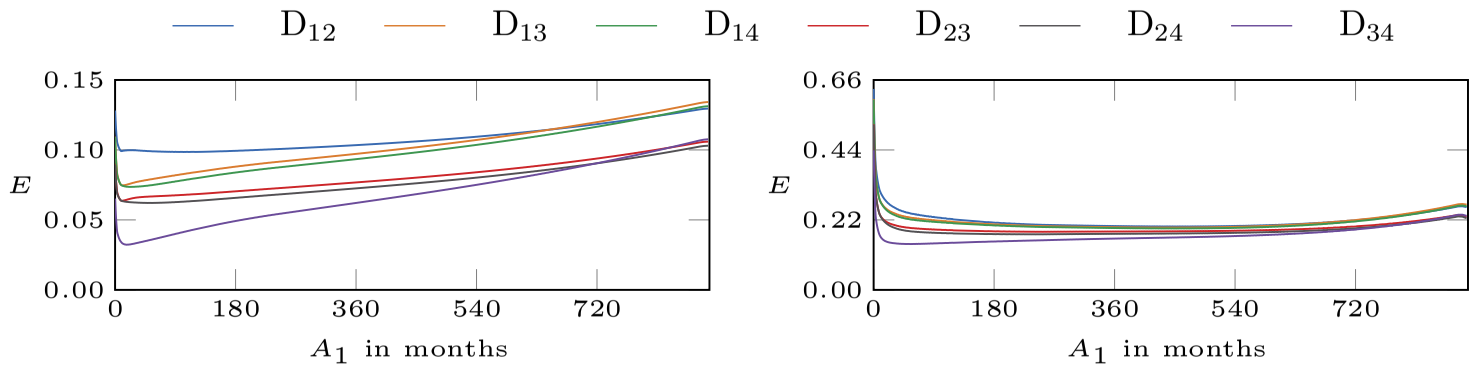
If primary infections are risk-free vaccination is not recommended as shown in Figures 6.8b and 6.8d for symptomatic and asymptomatic post-secondary in-

fections respectively. This is intuitive since in an endemic region with a single serotype in existence and risk-free primary infections there is zero lifetime expected risk. Vaccination causes some infections to be a secondary type infection and therefore risky and in addition if a seronegative individual is successfully vaccinated the vaccine increases the subsequent risk further. This is independent of whether two heterologous infections confer PCI. However, if there is PCI the differences in efficacy between the four serotypes are less relevant. Successful vaccination against any two serotypes means that the recipient will not experience a risky infection even after vaccination so that the overall efficacy is more decisive. In both CRSs the higher vaccine efficacy in combination with the lower force of infection again results in the lifetime expected risk being lowest for DENv4 if vaccination is carried out despite not being recommended.

In CRS (c) when primary infections are risky but post-secondary infections risk-free vaccination is also not always recommended. From Figure 6.8c it can be seen that again the high efficacy against DENv4 and the low force of infection result in the lowest lifetime expected risk. Similarly the relatively low efficacy and high force of infection for DENv1 result in the highest lifetime expected risk. However, the difference between the four serotypes is much smaller than in CRS (a) since the efficacy against any serotype can potentially decrease the risk due to post-secondary infections being free of risk. If third and fourth infections are asymptomatic the optimal vaccination ages for DENv3 and DENv4 are slightly increased to 17 and 56 months respectively. For DENv1 and DENv2 vaccination is no longer recommended at all.

From an endemic region with a single existing serotype it can therefore be seen that the vaccine-induced risk has a large impact on the outcome of vaccination. The efficacy against a specific serotype is decisive in whether vaccination is recommended if primary infections are risk-free. For a low efficacy against the endemic serotype and high efficacies against non-endemic serotypes there is a high risk of successfully vaccinating against serotypes that are not in circulation without preventing an infection with the endemic serotype. If many seronegatives are vaccinated this increases. If vaccination is delayed until less individuals are seronegative even fewer infections with the endemic serotype can be prevented and if primary infections are risky and third and fourth infections asymptomatic vaccination is no longer recommended if DENv1 or DENv2 is endemic.

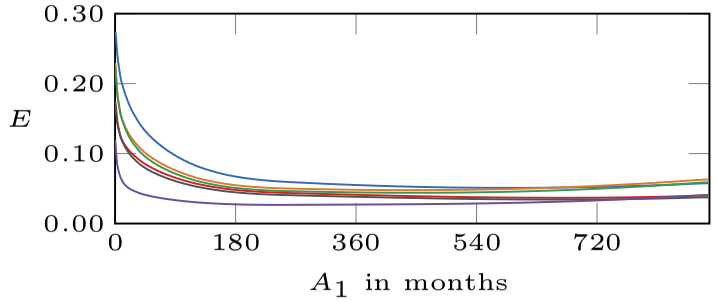
The results for an endemic region with two coexisting serotypes are presented in Figure 6.9. As before the subfigures correspond to the four CRSs. A vaccine-induced risk has an impact particularly if some of the infections are risk-free.



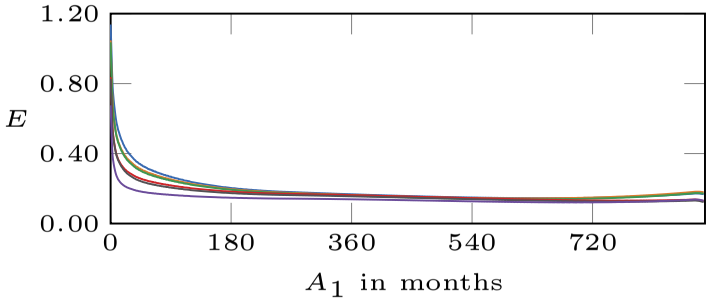

(a) The optimal vaccination ages for DENv12, DENv13, DENv14, DENv23, DENv24 and DENv34 are 102, 11, 23, 11, 48 and 17 months respectively.




(c) The optimal vaccination ages for DENv12, DENv13, DENv14, DENv23, DENv24 and DENv34 are 453, 445, 449, 253, 242 and 56 months respectively.




(b) The optimal vaccination ages for DENv12, DENv13, DENv14, DENv23, DENv24 and DENv34 are 589, 445, 449, 667, 640 and 242 months respectively.




(d) Vaccination is not recommended for DENv23 and DENv24. The optimal vaccination ages for DENv12, DENv13, DENv14 and DENv34 are 640, 618, 640 and 696 months respectively.

Figure 6.9: The lifetime expected risk $E$ of hospitalisation in an endemic area where two serotypes coexist as a function of age $A_1$ at which the first vaccine dose is administered. The vaccine efficacy is assumed serotype-specific but age-independent as given in Table 1.1. An age-independent vaccine-induced risk is considered as given in Table 1.2. The subfigures (a)–(d) correspond to the CRS (a)–(d) respectively.

In CRS (a) as shown in Figure 6.9a all infections are assumed risky. The optimal vaccination ages vary between 11 and 102 months with the highest optimal vaccination age for DENv12. The efficacy is more effective against DENv3 and DENv4 than DENv1 and DENv2. If vaccination takes place early in endemic regions with DENv1 and DENv2 when more infections can be prevented it is possible that many seronegatives will be vaccinated against a non-endemic serotype. Therefore they will experience a higher risk in a subsequent infection. It is better to wait until the likelihood of vaccinating a seronegative is smaller even if that means fewer infections can be prevented. The higher efficacy against at least one of the other serotypes for all other combinations leads to lower optimal vaccination ages since more infections will be prevented. Similarly to the case of no vaccine-induced risk there are two groups of combinations that can be distinguished in Figure 6.9a, i.e. those that do include DENv1 and those that do not. Combinations including DENv1 result in a higher lifetime expected risk due to the high force of infection of this serotype. Within the two groups those with a lower combined efficacy lead to a higher lifetime expected risk at almost all vaccination ages. However, at very high vaccination ages when the impact of vaccination will be very low the combined force of infection is decisive.

CRS (b) is presented in Figure 6.9b where it can be seen that with two coexisting serotypes vaccination can reduce the lifetime expected risk even if primary infections are risk-free. However, the vaccination ages are much higher than if primary infections are risky. They vary between 242 and 667 months. The highest optimal vaccination ages are obtained for serotype combinations including DENv2 and the lowest optimal vaccination age is that for DENv34 due to the very high efficacy against both serotypes. Independently of the serotype combination vaccination should take place once most primary infections have occurred. On one hand primary infections do not need to be targeted as they are risk-free and on the other hand successfully vaccinating seronegatives without successfully vaccinating against all endemic serotypes will increase the risk in infections that take place after vaccination. The lower the efficacy for the endemic serotypes and the higher the efficacy for the non-endemic ones the more likely it will be to vaccinate against non-endemic serotypes only. This results in higher optimal vaccination ages for combinations including DENv2 due to the vaccine being fairly ineffective against this serotype.

The results for two heterologous infections conferring PCI are shown in Figure 6.9c. Again the optimal vaccination ages are significantly higher than in CRS (a). For serotype combinations including DENv1 they vary little and lie

between 445 and 453 months. If DENv1 is not endemic the optimal vaccination age is much lower between 56 and 253 months. In this case the higher optimal vaccination ages of 253 and 242 months are obtained when DENv2 is endemic. In CRS (c) primary infections are symptomatic so that if sufficient infections can be prevented vaccination should take place before many primary infections occur. This is the case if DENv3 and DENv4 coexist due to the high efficacy for these two serotypes. However, if too many seronegative individuals are successfully vaccinated against only one serotype it is better to vaccinate later when fewer seronegatives are targeted. With the high force of infection of DENv1 but relatively low efficacy this is particularly pronounced if this serotype is endemic. DENv1 causes more infections than the remaining serotypes but only few of those can be prevented. Vaccinating more seropositives has the advantage of reducing the probability of vaccine-induced risk. In addition if seropositives who have had one infection are targeted it is sufficient to successfully vaccinate against any serotype the individual was not infected with to eliminate all further risk. This also results in there being much less difference between the lifetime expected risk caused by any serotype combination since successfully vaccinating against non-endemic serotypes can also reduce the risk.

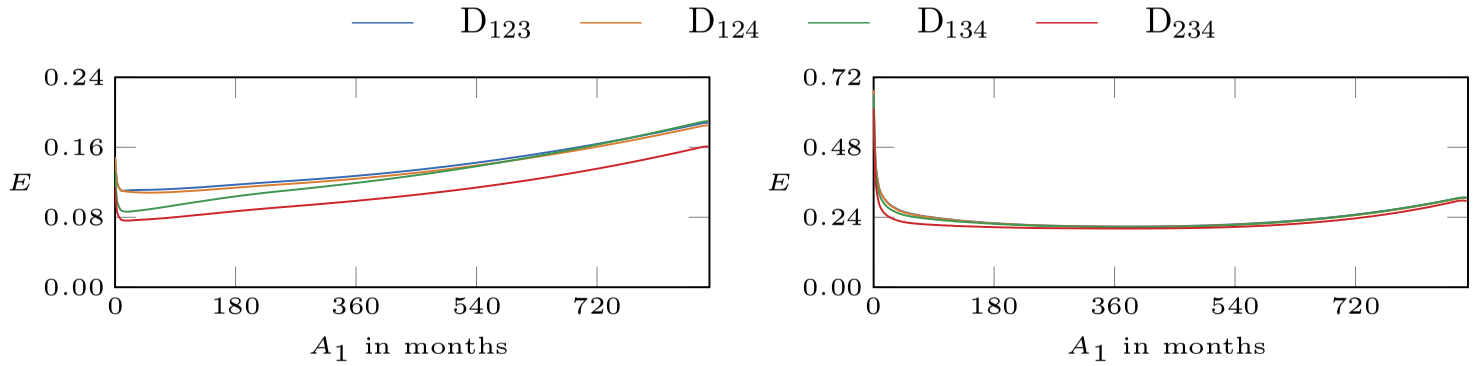
In the previous chapter CRS (c) and CRS (d) resulted in the same optimal vaccination age in almost every case for several coexisting serotypes. This was caused by the force of infection and thus infection probability tending to zero at higher ages. With the force of infection that was derived from serological data there is a residual probability of getting infected at older ages. Primary infections are risk-free in CRS (d) so that these infections do not need to be targeted and should not be targeted so as to prevent vaccine-induced risk. In fact the only risky infection that needs to be targeted is the second one. If seronegatives are vaccinated the risk in the subsequent infection can be even higher and if vaccination takes place after the secondary infection it no longer has any effect. The ideal time to vaccinate would therefore be between the primary and secondary infection. However, not every individual will get infected at the same age and some individuals may still be seronegative at high ages. Due to the residual force of infection they are still at risk. It is therefore difficult to balance the increased risk in seronegative recipients with the number of prevented risky infections in seropositives. This can be seen from the fact that once mainly seropositives are vaccinated, i.e. at high vaccination ages, the lifetime expected risk is very flat. For DENv23 and DENv24 vaccination is in fact not recommended. The optimal vaccination ages for the remaining serotype combinations are very high between

618 and 696 months. The two groups including DENv1 and excluding DENv1 can still be observed but there is again less difference as effective vaccination against any two serotypes can reduce the number of risky infections.

For two coexisting serotypes the most decisive factor for the optimal vaccination age is therefore still the considered CRS. However, in each CRS the exact combination of the serotypes is very relevant. For risky primary infections and risk-free post-secondary infections the presence of DENv1 increases the optimal vaccination age significantly. For risk-free primary infections there is also a wide range in optimal vaccination ages and vaccination is not recommended at all for DENv23 and DENv24 if two heterologous infections confer PCI.

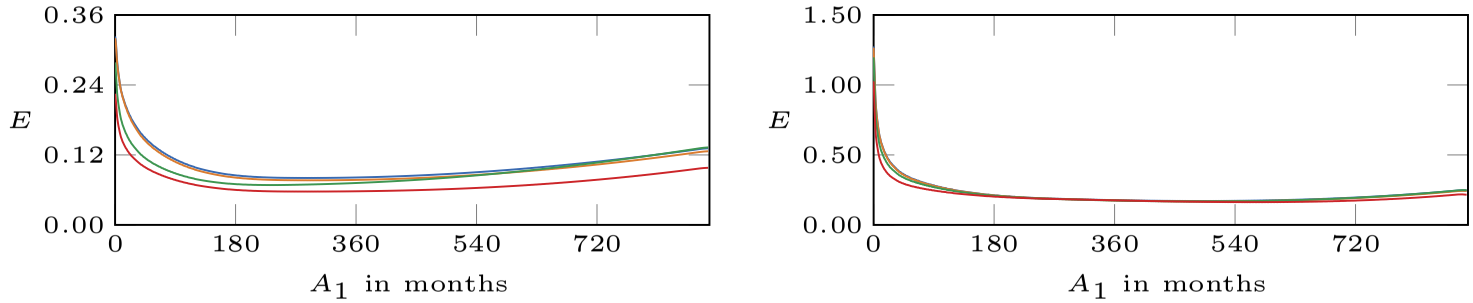
The results for three and four coexisting serotypes are presented in Figures 6.10 and 6.11 respectively. For three coexisting serotypes the highest risk is again caused by serotype combinations including DENv1 due to the high force of infection for this serotype. This is the case independently of the considered CRS even though for asymptomatic post-secondary infections the difference in lifetime expected risk is smaller.

In Figures 6.10a and 6.11a all infections are risky. Again the optimal vaccination ages are low, between 11 and 48 months for any serotype combination with three or four coexisting serotypes. In CRS (b) the optimal vaccination ages are much higher between 212 and 296 months. This is again due to the fact that primary infections do not have to be targeted since they are risk-free and should not be targeted since successful vaccination of seronegative individuals will increase their risk in subsequent infections. It is therefore essential to delay vaccination until most individuals have had one infection. Note that the more serotypes coexist the lower the optimal vaccination age in this case since a higher number of serotypes corresponds to a lower average age of infection overall. A similar observation can be made in CRS (d) where optimal vaccination ages for three serotypes lie between 491 and 571 months, while for four serotypes the optimal vaccination age is 411 months. In CRS (c) the situation is slightly more complicated. In endemic regions with three serotypes vaccination is ideal at 384 months, while for four serotypes it is ideal at 343 months. Compared to two endemic serotypes whether the optimal vaccination age increases or decreases therefore depends on which two serotypes exist in the two serotype case and which additional serotype is introduced. Compared to CRS (d) the optimal vaccination age is lower since primary infections are risky and even if some individuals are still seronegative it is better to vaccinate slightly earlier.




(a) The optimal vaccination ages for DENv123, DENv124, DENv134 and DENv234 are 11, 48, 17 and 17 months respectively.

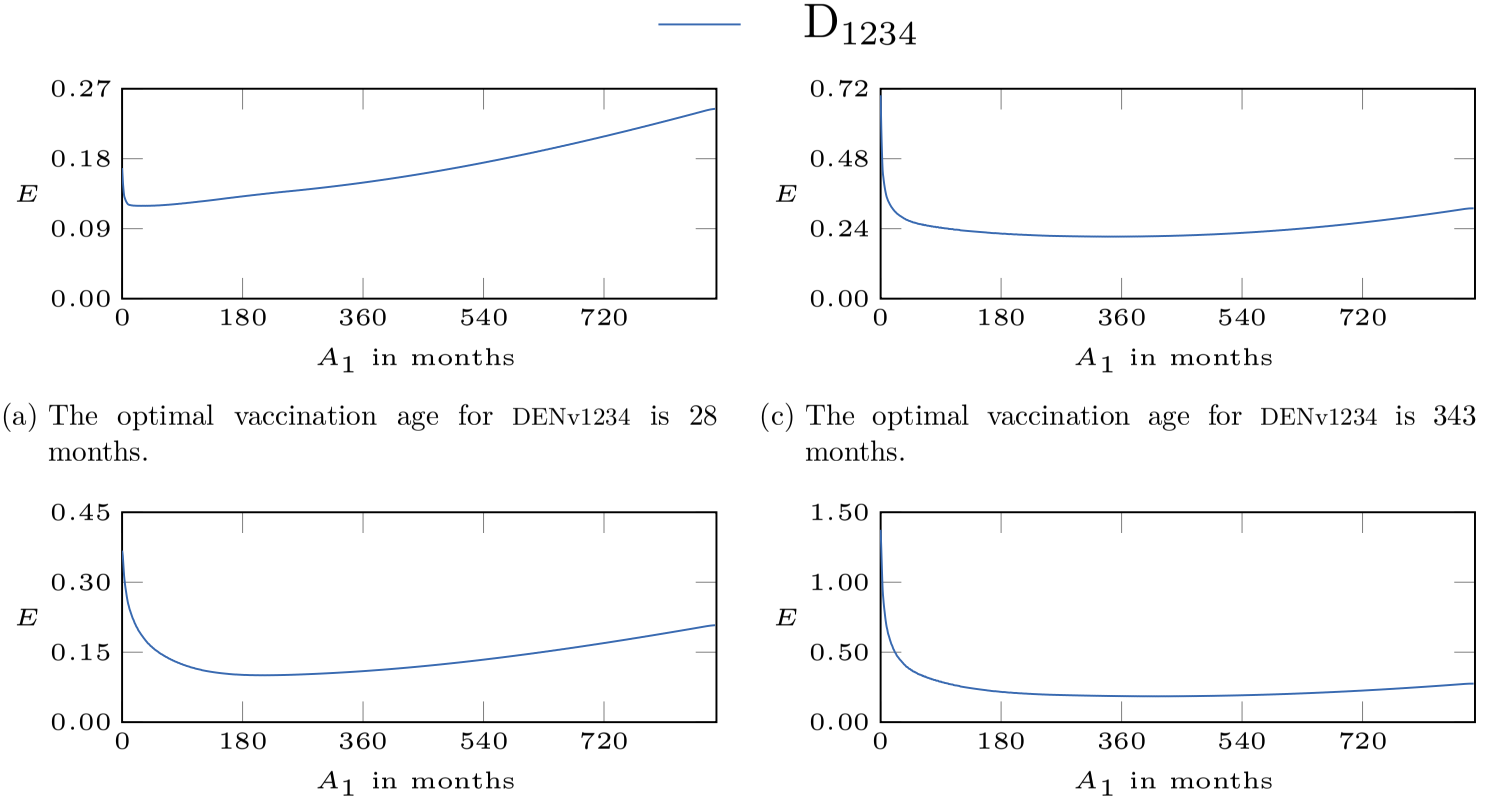
(c) The optimal vaccination age is 384 months for DENv123, DENv124, DENv134 and DENv234.




(b) The optimal vaccination ages for DENv123, DENv124, DENv134 and DENv234 are 287, 296, 242 and 287 months respectively.

(d) The optimal vaccination ages for DENv123, DENv124, DENv134 and DENv234 are 491, 499, 491 and 571 months respectively.

Figure 6.10: The lifetime expected risk $E$ of hospitalisation in an endemic area where three serotypes coexist as a function of age $A_1$ at which the first vaccine dose is administered. The vaccine efficacy is assumed serotype-specific but age-independent as given in Table 1.1. An age-independent vaccine-induced risk is considered as given in Table 1.2. The subfigures (a)–(d) correspond to the CRS (a)–(d) respectively.




(a) The optimal vaccination age for DENv1234 is 28 months.

(c) The optimal vaccination age for DENv1234 is 343 months.

(b) The optimal vaccination age for DENv1234 is 212 months.

(d) The optimal vaccination age for DENv1234 is 411 months.

Figure 6.11: The lifetime expected risk $E$ of hospitalisation in an endemic area where all four serotypes coexist as a function of age $A_1$ at which the first vaccine dose is administered. The vaccine efficacy is assumed serotype-specific but age-independent as given in Table 1.1. An age-independent vaccine-induced risk is considered as given in Table 1.2. The subfigures (a)–(d) correspond to the CRS (a)–(d) respectively.

Table 6.5: The optimal vaccination age $A_1$ in months which minimises the lifetime expected risk $E$ of hospitalisation for all CRSs. The vaccine efficacy is assumed serotype-specific but age-independent as given in Table 1.1. An age-independent vaccine-induced risk is considered as given in Table 1.2. '–' represents cases in which vaccination is not recommended, i.e. when $A_1$ was found to be above a reasonable age for humans.

| | CRS (a) | | CRS (b) | | CRS (c) | | CRS (d) | |
|---|---|---|---|---|---|---|---|---|
| | $A_1$ | $E_{\times 10^{-2}}$ | $A_1$ | $E_{\times 10^{-2}}$ | $A_1$ | $E_{\times 10^{-2}}$ | $A_1$ | $E_{\times 10^{-2}}$ |
| DENv1 | 9 | 6.12 | – | 0.00 | – | 12.37 | – | 0.00 |
| DENv2 | 182 | 4.81 | – | 0.00 | – | 9.65 | – | 0.00 |
| DENv3 | 12 | 1.73 | – | 0.00 | 17 | 8.75 | – | 0.00 |
| DENv4 | 32 | 1.50 | – | 0.00 | 56 | 6.83 | – | 0.00 |
| DENv12 | 102 | 9.85 | 589 | 5.09 | 453 | 19.91 | 640 | 14.43 |
| DENv13 | 11 | 7.47 | 445 | 4.77 | 445 | 19.57 | 618 | 14.32 |
| DENv14 | 23 | 7.36 | 449 | 4.39 | 449 | 19.30 | 640 | 13.82 |
| DENv23 | 11 | 6.37 | 667 | 3.68 | 253 | 18.25 | – | 12.86 |
| DENv24 | 48 | 6.21 | 640 | 3.43 | 242 | 17.46 | – | 12.30 |
| DENv34 | 17 | 3.23 | 242 | 2.66 | 56 | 14.41 | 696 | 12.05 |
| DENv123 | 11 | 11.03 | 287 | 8.05 | 384 | 20.79 | 491 | 17.05 |
| DENv124 | 48 | 10.80 | 296 | 7.65 | 384 | 20.72 | 499 | 16.79 |
| DENv134 | 17 | 8.63 | 242 | 6.83 | 384 | 20.63 | 491 | 16.72 |
| DENv234 | 17 | 7.61 | 287 | 5.72 | 384 | 20.12 | 571 | 16.24 |
| DENv1234 | 28 | 11.94 | 212 | 10.05 | 343 | 21.27 | 411 | 18.47 |

A summary of all optimal vaccination ages and the minimal lifetime expected risk is given in Table 6.5. Clearly the optimal vaccination ages vary significantly with the considered CRS. They are lowest in CRS (a) and highest in CRS (d). For three and four coexisting serotypes it increases as the number of risky infections decreases, i.e. the optimal vaccination age obtained in CRS (c) is higher than that obtained in CRS (b). Additionally the specific endemic serotypes are relevant. The high force of infection for DENv1 leads to a higher minimal lifetime expected risk independently of the CRS and the number of coexisting serotypes. The low efficacy against DENv2 can also have a large impact. For DENv23 and DENv24 in CRS (d) vaccination is not recommended since too few infections can be prevented and the risk can be increased if seronegatives are successfully vaccinated against only one of the endemic serotypes. Vaccination is also not recommended if only DENv1 or DENv2 is endemic if CRS (c) is most realistic. This is again caused by the vaccine being less effective against these serotypes compared to DENv3 and DENv4. This demonstrates the importance of the vaccine efficacy but also of determining which serotypes are present before a vaccination campaign is initiated.

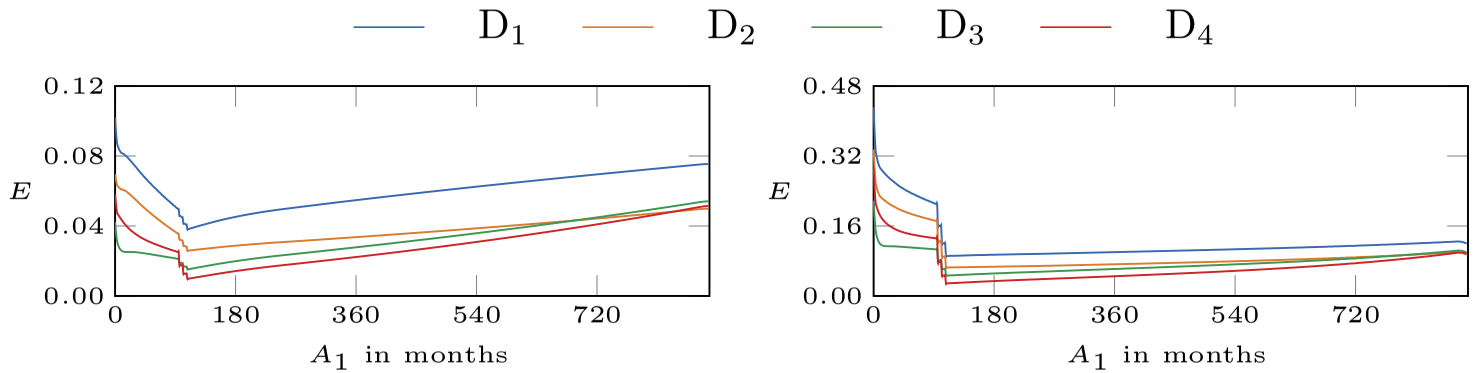
### Age-Dependent Vaccine Efficacy and Vaccine-Induced Risk

During the vaccine trial the efficacy and the number of hospitalisations was recorded for the two age-groups of participants below 9 years and 9 years and older. The results considering these age-groups will therefore briefly be discussed so as to highlight the effect the age-dependence of the efficacy and vaccine-induced risk has on the optimal vaccination ages. The summary of the optimal vaccination age and minimal lifetime expected risk for this case is presented in Table 6.6.

Assuming an age-dependent efficacy according to Table 1.1 results in a lower efficacy for children under the age of 9 years compared to the pooled efficacy and a higher one for older children. Similarly an age-dependent vaccine-induced risk based on the recorded number of hospitalisations in the two age-groups as shown in Table 1.2 results in a higher risk in younger and a lower risk in older children. It is therefore not surprising that particularly if primary infections are risky the lower vaccine-induced risk and higher probability of effectively vaccinating against any serotype in older ages leads to a significant increase in optimal vaccination age. In fact, in CRS (a) and CRS (c) vaccination is ideal at 9 years independently of

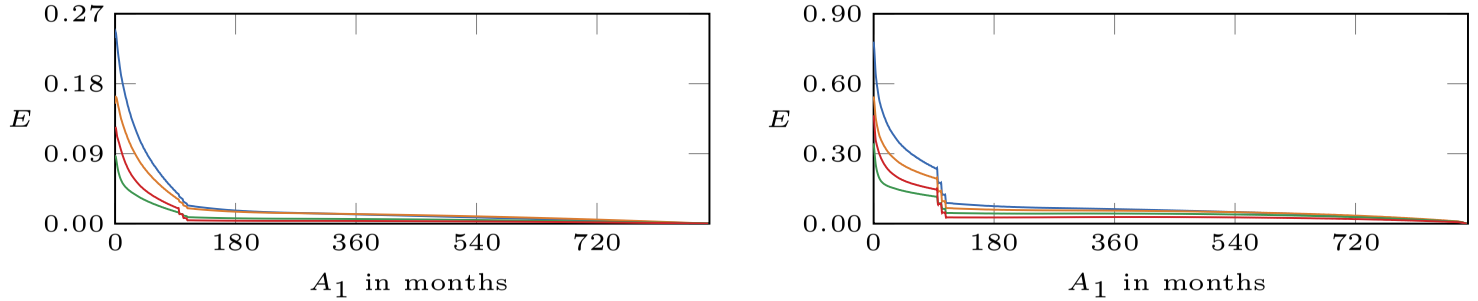
Table 6.6: The optimal vaccination age $A_1$ in months which minimises the lifetime expected risk $E$ of hospitalisation for all CRSs. The vaccine efficacy is assumed serotype-specific and age-dependent as given in Table 1.1. An age-dependent vaccine-induced risk is considered as given in Table 1.2. '–' represents cases in which vaccination is not recommended, i.e. when $A_1$ was found to be above a reasonable age for humans.

| | CRS (a) | | CRS (b) | | CRS (c) | | CRS (d) | |
|---|---|---|---|---|---|---|---|---|
| | $A_1$ | $E_{\times 10^{-2}}$ | $A_1$ | $E_{\times 10^{-2}}$ | $A_1$ | $E_{\times 10^{-2}}$ | $A_1$ | $E_{\times 10^{-2}}$ |
| DENv1 | 108 | 3.80 | – | 0.00 | 109 | 9.13 | – | 0.00 |
| DENv2 | 108 | 2.59 | – | 0.00 | 109 | 6.51 | – | 0.00 |
| DENv3 | 108 | 1.51 | – | 0.00 | 109 | 4.66 | – | 0.00 |
| DENv4 | 108 | 0.97 | – | 0.00 | 108 | 2.87 | – | 0.00 |
| DENv12 | 108 | 5.93 | 253 | 3.57 | 109 | 11.31 | 384 | 8.72 |
| DENv13 | 108 | 5.13 | 206 | 3.05 | 109 | 10.88 | 347 | 8.60 |
| DENv14 | 108 | 4.69 | 212 | 2.63 | 109 | 10.41 | 384 | 8.17 |
| DENv23 | 108 | 3.93 | 253 | 2.38 | 109 | 9.06 | 407 | 7.77 |
| DENv24 | 108 | 3.47 | 242 | 2.07 | 109 | 8.18 | 392 | 7.10 |
| DENv34 | 108 | 2.46 | 165 | 1.33 | 108 | 6.88 | 242 | 6.35 |
| DENv123 | 108 | 7.18 | 165 | 5.35 | 109 | 12.33 | 253 | 10.51 |
| DENv124 | 108 | 6.78 | 165 | 4.90 | 109 | 12.10 | 253 | 10.24 |
| DENv134 | 108 | 6.02 | 138 | 4.21 | 109 | 11.82 | 253 | 10.13 |
| DENv234 | 108 | 4.81 | 165 | 3.33 | 109 | 10.34 | 253 | 9.16 |
| DENv1234 | 108 | 8.03 | 119 | 6.50 | 109 | 12.94 | 212 | 11.85 |




(a) The optimal vaccination age is 108 months for DENv1, DENv2, DENv3 and DENv4.

(c) The optimal vaccination ages for DENv1, DENv2, DENv3 and DENv4 are 109, 109, 109 and 108 months respectively.




(b) Vaccination is not recommended for any serotype.

(d) Vaccination is not recommended for any serotype.

Figure 6.12: The lifetime expected risk $E$ of hospitalisation in an endemic area where a single serotype exists as a function of age $A_1$ at which the first vaccine dose is administered. The vaccine efficacy is assumed serotype-specific and age-dependent as given in Table 1.1. An age-dependent vaccine-induced risk is considered as given in Table 1.2. The subfigures (a)–(d) correspond to the CRS (a)–(d) respectively.

the number or combination of serotypes. In CRS (b) and CRS (d), when primary infections are risk-free, the age-dependence has less impact. However, overall the optimal vaccination age is decreased. This is due to more infections being prevented if the efficacy is higher. Additionally the lower induced risk means that even if more seronegatives are vaccinated in such a way that they will experience a higher risk the aggregate risk is lower. Vaccination can then take place earlier to prevent more infections even if fewer individuals are seropositive.

In the case of no vaccine-induced risk when the risk of hospitalisation is minimised it was already seen that the increase in efficacy leads to drops at the vaccination ages of 96, 102 and 108 months. In Figure 6.12 this can also be observed for an endemic area with a single serotype in circulation when the vaccine induces a higher risk in some recipients. By comparing Figures 6.8 and 6.12 it can be seen that apart from this most observations are very similar particularly if not all infections are risky. In CRS (a) and CRS (c) the increase in efficacy and the decrease in risk at 9 years significantly impacts the optimal vaccination age and raises it or lowers it to 9 years. In CRS (b) and CRS (d) the drops can still be observed but since the lifetime expected risk is zero without vaccination this has no impact and vaccination is still not recommended. The corresponding optimal vaccination age and minimal lifetime expected risk for any combination of several coexisting serotypes is only given in Table 6.6 but not discussed in more detail since the drops have similar effects.

### Licence Restrictions

Only individuals aged 9 to 45 years can receive Dengvaxia in Brazil. A vaccine-induced risk results in optimal vaccination ages that often adhere to the current age restriction. In fact, if the vaccine-induced risk and vaccine efficacy are assumed to be age-dependent the optimal vaccination ages are all within the permitted age-range as long as vaccination is recommended. In this case the restriction therefore has no negative effect whatsoever which is unsurprising considering that the age-range was chosen based on the age-group dependent trial data.

If the age-groups from the Dengvaxia trial are disregarded there are a significant number of scenarios that require vaccination below the age of 9 years, particularly in CRS (a). On the other hand, in CRS (d) many optimal vaccination ages are above the maximum age of 45 years. Restricting the vaccination ages in such a way that all three doses are administered within the permitted age-range leads to an increase in the lifetime expected risk that can be achieved compared to the minimal one. In particular the percentage increase for each scenario that

is ideally targeted outwith the age-range of 9 to 45 years and the corresponding restricted optimal age are presented in Table 6.7. Clearly vaccination should take place as close as possible to the ideal vaccination age, i.e. at 9 years if the optimal age is below 9 years and at 45 years if it is above the maximum age. The percentage increase is fairly limited and no higher than 46%. If vaccination is not recommended there is an exception to this rule. If only DENv2 is endemic in CRS (c) the best time to vaccinate according to the current licence restriction is at 242 months resulting in a percentage increase of 45%. Compared to no vaccine-induced risk these increases are much lower. Since more optimal ages are nearer to the permitted age-range the age-restriction has much less effect if the vaccine induces a higher risk in some recipients than if naturally acquired and vaccine-induced antibodies behave the same way. Nonetheless it might be better to permit vaccination of seropositives at any age if the age-dependence of the

Table 6.7: The vaccination age $A_1$ in months which lies within the permitted age-range for the vaccine and minimises the lifetime expected risk $E$ of hospitalisation. The percentage increase from the optimal lifetime expected risk $\delta_E\%$ is given for any case in which the optimal vaccination age lies outwith the permitted age-range of Dengvaxia. For cases in which vaccination is not recommended and the minimal lifetime expected risk is zero the percentage increase is given by $\infty$. The vaccine efficacy is assumed serotype-specific but age-independent as given in Table 1.1. An age-independent vaccine-induced risk is considered as given in Table 1.2.

| | CRS (a) | | CRS (b) | | CRS (c) | | CRS (d) | |
|---|---|---|---|---|---|---|---|---|
| | $A_1$ | $\delta_E\%$ | $A_1$ | $\delta_E\%$ | $A_1$ | $\delta_E\%$ | $A_1$ | $\delta_E\%$ |
| DENv1 | 109 | 7 | 538 | $\infty$ | 538 | 36 | 538 | $\infty$ |
| DENv2 | 182 | – | 538 | $\infty$ | 242 | 45 | 538 | $\infty$ |
| DENv3 | 108 | 46 | 538 | $\infty$ | 109 | 9 | 538 | $\infty$ |
| DENv4 | 108 | 25 | 538 | $\infty$ | 109 | 5 | 538 | $\infty$ |
| DENv12 | 109 | $< 1$ | 538 | $< 1$ | 453 | – | 538 | 3 |
| DENv13 | 108 | 11 | 445 | – | 445 | – | 538 | 2 |
| DENv14 | 108 | 7 | 449 | – | 449 | – | 538 | 2 |
| DENv23 | 109 | 7 | 538 | 2 | 253 | – | 538 | 13 |
| DENv24 | 108 | 2 | 538 | 2 | 242 | – | 538 | 13 |
| DENv34 | 108 | 30 | 242 | – | 109 | 2 | 538 | 5 |
| DENv123 | 109 | 3 | 287 | – | 384 | – | 491 | – |
| DENv124 | 109 | 2 | 296 | – | 384 | – | 499 | – |
| DENv134 | 108 | 11 | 242 | – | 384 | – | 491 | – |
| DENv234 | 108 | 7 | 287 | – | 384 | – | 538 | $< 1$ |
| DENv1234 | 108 | 4 | 212 | – | 343 | – | 411 | – |

efficacy and vaccine-induced risk are actually only due to the serostatus and not due to the age per se.

### 6.4.3 Minimising the Risk of Lethality

Another indicator of the burden of dengue in Brazil is the number of deaths it causes. Vaccination can be employed in such a way that the risk of lethality is minimised. In fact the risk of lethality is very similar to that of hospitalisation with the exception that the risk of lethality at old ages far over-shadows the risk for children. For a force of infection with zero residual there was found to be very little difference between the optimal vaccination strategies for the two risk functions in the previous chapter. The question that will be answered in this section is therefore whether the non-zero residual force of infection for older individuals and the very high risk of lethality at these ages impact at which age vaccination should be carried out.

#### Constant Vaccine Efficacy

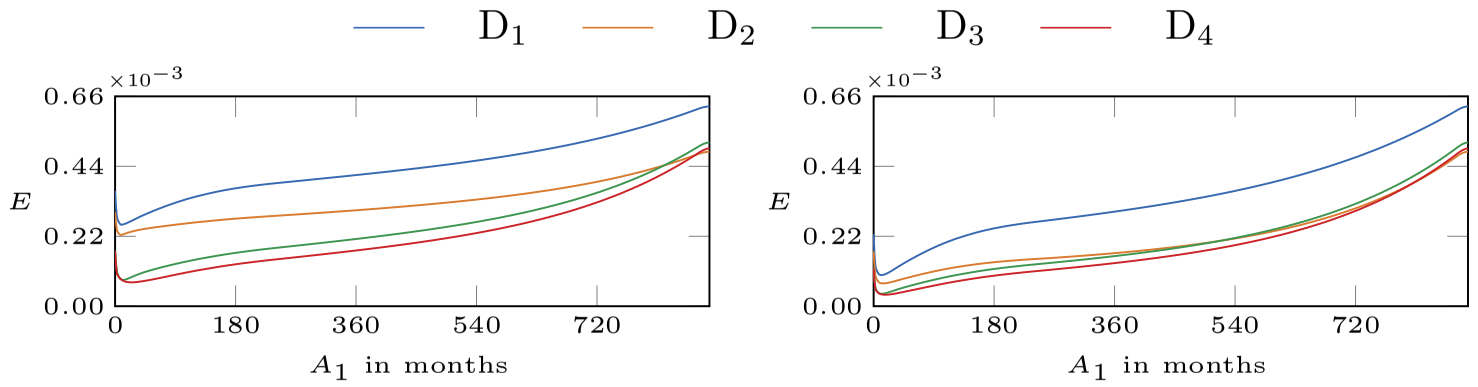
The optimal vaccination ages to minimise the risk of lethality when the vaccine efficacy is assumed constant are presented in Table 6.8. Clearly the optimal vaccination ages in CRS (a) and CRS (c) i.e. when primary infections are risky, are very low between 9 and 17 months with the sole exception of DENv4 in CRS (c) when it is 23 months. For the risk of hospitalisation these ages are similarly low as can be noted by comparing the results to those for the risk of hospitalisation as summarised in Table 6.1. In CRS (b) and CRS (d) the optimal vaccination ages vary much more and lie between 56 and 219 months. They are still very similar to those obtained for the risk of hospitalisation. However, in CRS (b) a small decrease can be observed while in CRS (d) in most cases the optimal vaccination age increases compared to that obtained for the risk of hospitalisation. Other observations such as the decreasing age with an increasing number of serotypes in CRS (b) and CRS (d), or the increase in minimal lifetime expected risk as the number of serotypes increases have the same reasons as for the risk of hospitalisation.

In summary there is therefore very little difference between the two risk functions. Nonetheless we will briefly consider a region with a single endemic serotype for the risk of lethality as shown in Figure 6.13. In comparison to Figure 6.3 it becomes clear that not only are the optimal vaccination ages for both risk functions similar, even the behaviour of the lifetime expected risk is little influenced by the differences between the two risk functions. Again the serotype-specific

Table 6.8: The optimal vaccination age $A_1$ in months which minimises the lifetime expected risk $E$ of lethality for all CRSs. The vaccine efficacy is assumed serotype-specific but age-independent as given in Table 1.1. '–' represents cases in which vaccination is not recommended, i.e. when $A_1$ was found to be above a reasonable age for humans.

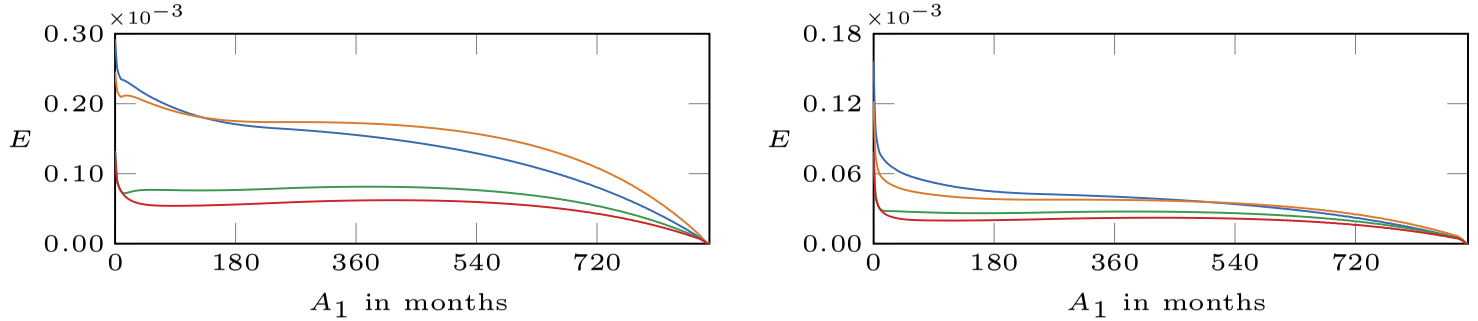
| | CRS (a) | | CRS (b) | | CRS (c) | | CRS (d) | |
|---|---|---|---|---|---|---|---|---|
| | $A_1$ | $E_{\times 10^{-5}}$ | $A_1$ | $E_{\times 10^{-5}}$ | $A_1$ | $E_{\times 10^{-5}}$ | $A_1$ | $E_{\times 10^{-5}}$ |
| DENv1 | 9 | 25.63 | – | 0.00 | 11 | 9.81 | – | 0.00 |
| DENv2 | 9 | 22.38 | – | 0.00 | 14 | 7.18 | – | 0.00 |
| DENv3 | 12 | 8.28 | – | 0.00 | 12 | 3.92 | – | 0.00 |
| DENv4 | 23 | 7.51 | – | 0.00 | 17 | 3.60 | – | 0.00 |
| DENv12 | 9 | 48.01 | 219 | 37.32 | 11 | 13.52 | 119 | 7.61 |
| DENv13 | 11 | 33.96 | 182 | 27.35 | 11 | 12.15 | 102 | 7.24 |
| DENv14 | 14 | 33.69 | 182 | 24.84 | 12 | 12.00 | 102 | 6.89 |
| DENv23 | 10 | 30.79 | 165 | 26.55 | 14 | 9.87 | 119 | 6.06 |
| DENv24 | 14 | 30.58 | 165 | 24.24 | 14 | 9.64 | 119 | 5.68 |
| DENv34 | 17 | 16.12 | 63 | 13.49 | 14 | 7.16 | 70 | 4.67 |
| DENv123 | 10 | 56.43 | 144 | 48.38 | 11 | 14.93 | 63 | 9.08 |
| DENv124 | 11 | 56.33 | 146 | 45.76 | 11 | 14.82 | 70 | 8.87 |
| DENv134 | 14 | 42.00 | 109 | 34.94 | 11 | 13.84 | 63 | 8.57 |
| DENv234 | 14 | 38.90 | 119 | 33.51 | 14 | 11.92 | 76 | 7.51 |
| DENv1234 | 11 | 64.61 | 102 | 56.08 | 11 | 15.90 | 56 | 9.85 |

force of infection and the vaccine efficacy determine how high the burden caused by any serotype is in comparison to the remaining serotypes. The force of infection for DENv1 is highest with a low efficacy so that this serotype results in the highest lifetime expected risk independently of vaccination age if primary infections are risky. The remaining serotypes have a similar force of infection but Dengvaxia is much more effective against DENv4 than DENv2 so that the lowest risk is due to DENv4 for almost all vaccination ages independently of CRS. All other observations for a single endemic serotype are also entirely transferable to the risk of lethality. This is also the case for several coexisting serotypes so that the remaining results for lethality will be omitted. Note, however, that compared to the risk of hospitalisation the lifetime expected risk is much lower.




(a) The optimal vaccination ages for DENv1, DENv2, DENv3 and DENv4 are 9, 9, 12 and 23 months respectively.

(c) The optimal vaccination ages for DENv1, DENv2, DENv3 and DENv4 are 11, 14, 12 and 17 months respectively.




(b) Vaccination is not recommended for any serotype.

(d) Vaccination is not recommended for any serotype.

Figure 6.13: The lifetime expected risk $E$ of lethality in an endemic area where a single serotype exists as a function of age $A_1$ at which the first vaccine dose is administered. The vaccine efficacy is assumed serotype-specific but age-independent as given in Table 1.1. The subfigures (a)–(d) correspond to the CRS (a)–(d) respectively.

### Age-Dependent Vaccine Efficacy

The assumption of an age-dependent efficacy when the risk of lethality is minimised and when the risk of hospitalisation is minimised has very similar effects. This effect was discussed for hospitalisation based on an endemic area with a single serotype. The main difference to the constant efficacy case was the drops in lifetime expected risk once one of the three doses is given to individuals aged 9 years or above, i.e. when the first dose is given at 96, 102 or 108 months. These drops have in fact only a small impact on the optimal vaccination age for many considered scenarios when hospitalisation is considered. From Table 6.9 it can be seen that more serotype combinations are affected for the risk of lethality. The optimal vaccination ages that are impacted by the efficacy assumption increase to 9 years if they are far below 9 years in most cases in CRS (a) and CRS (c). In CRS (d) vaccination ages that are slightly above 9 years in the constant efficacy case decrease to 9 years while the remaining ages increase. In CRS (b) the optimal vaccination ages are fairly similar for both efficacy assumptions. In CRS (d) the only infection that needs to be targeted is the secondary infection. Considering that the efficacy significantly increases at 9 years and that most secondary in-

Table 6.9: The optimal vaccination age $A_1$ in months which minimises the lifetime expected risk $E$ of lethality for all CRSs. The vaccine efficacy is assumed serotype-specific and age-dependent as given in Table 1.1. '–' represents cases in which vaccination is not recommended, i.e. when $A_1$ was found to be above a reasonable age for humans.

| | CRS (a) | | CRS (b) | | CRS (c) | | CRS (d) | |
|---|---|---|---|---|---|---|---|---|
| | $A_1$ | $E_{\times 10^{-5}}$ | $A_1$ | $E_{\times 10^{-5}}$ | $A_1$ | $E_{\times 10^{-5}}$ | $A_1$ | $E_{\times 10^{-5}}$ |
| DENv1 | 10 | 31.29 | – | 0.00 | 108 | 18.06 | – | 0.00 |
| DENv2 | 108 | 24.09 | – | 0.00 | 108 | 10.10 | – | 0.00 |
| DENv3 | 12 | 12.74 | – | 0.00 | 108 | 8.19 | – | 0.00 |
| DENv4 | 108 | 8.28 | – | 0.00 | 108 | 5.77 | – | 0.00 |
| DENv12 | 108 | 55.69 | 212 | 34.50 | 108 | 25.71 | 109 | 5.88 |
| DENv13 | 11 | 44.07 | 165 | 25.39 | 14 | 24.32 | 109 | 5.59 |
| DENv14 | 108 | 39.89 | 168 | 21.63 | 108 | 23.01 | 109 | 5.18 |
| DENv23 | 108 | 37.34 | 159 | 24.52 | 108 | 17.12 | 109 | 4.59 |
| DENv24 | 108 | 32.37 | 159 | 20.99 | 108 | 15.24 | 109 | 4.10 |
| DENv34 | 108 | 21.54 | 109 | 11.32 | 108 | 13.66 | 109 | 3.44 |
| DENv123 | 108 | 68.95 | 135 | 44.55 | 14 | 29.65 | 109 | 7.47 |
| DENv124 | 108 | 63.98 | 139 | 40.67 | 14 | 30.10 | 109 | 7.13 |
| DENv134 | 108 | 53.15 | 109 | 30.78 | 14 | 28.95 | 109 | 6.90 |
| DENv234 | 108 | 45.63 | 109 | 29.40 | 108 | 21.97 | 109 | 5.76 |
| DENv1234 | 108 | 77.23 | 109 | 50.04 | 14 | 31.93 | 108 | 8.71 |

fection will occur later it is therefore reasonable to administer the vaccine once the efficacy is higher and capable of preventing more infections even if a few secondary infections have already occurred. In CRS (a) all infections are risky but the age-dependent efficacy is much lower than the pooled one so that with the lower efficacy fewer infections can be prevented and it is often better to delay vaccination until the vaccine becomes more effective in the recipients.

### Licence Restrictions

Many optimal vaccination ages are outwith the age-range of 9 to 45 years when the risk of lethality is being targeted by vaccination especially if the vaccine efficacy is age-independent. Considering that Dengvaxia cannot be administered to children below the age of 9 years it is necessary to restrict the vaccination age based on the licensed age-range. Tables 6.10 and 6.11 present the ages at which

Table 6.10: The vaccination age $A_1$ in months which lies within the permitted age-range for the vaccine and minimises the lifetime expected risk $E$ of lethality. The percentage increase from the optimal lifetime expected risk $\delta_E\%$ is given for any case in which the optimal vaccination age lies outwith the permitted age-range of Dengvaxia. For cases in which vaccination is not recommended the minimal lifetime expected risk is zero, so that the percentage increase is given by $\infty$. The vaccine efficacy is assumed serotype-specific but age-independent as given in Table 1.1.

| | CRS (a) | | CRS (b) | | CRS (c) | | CRS (d) | |
|---|---|---|---|---|---|---|---|---|
| | $A_1$ | $\delta_E\%$ | $A_1$ | $\delta_E\%$ | $A_1$ | $\delta_E\%$ | $A_1$ | $\delta_E\%$ |
| DENv1 | 108 | 32 | 538 | $\infty$ | 108 | 104 | 538 | $\infty$ |
| DENv2 | 108 | 17 | 538 | $\infty$ | 108 | 63 | 538 | $\infty$ |
| DENv3 | 108 | 71 | 123 | $\infty$ | 108 | 133 | 165 | $\infty$ |
| DENv4 | 108 | 42 | 109 | $\infty$ | 108 | 101 | 119 | $\infty$ |
| DENv12 | 108 | 25 | 219 | – | 108 | 110 | 119 | – |
| DENv13 | 108 | 41 | 182 | – | 108 | 124 | 109 | $< 1$ |
| DENv14 | 108 | 32 | 182 | – | 108 | 116 | 109 | $< 1$ |
| DENv23 | 108 | 31 | 165 | – | 108 | 96 | 119 | – |
| DENv24 | 108 | 20 | 165 | – | 108 | 85 | 119 | – |
| DENv34 | 108 | 54 | 109 | 1 | 108 | 122 | 109 | 2 |
| DENv123 | 108 | 31 | 144 | – | 108 | 132 | 109 | 4 |
| DENv124 | 108 | 25 | 146 | – | 108 | 126 | 109 | 3 |
| DENv134 | 108 | 39 | 109 | – | 108 | 134 | 109 | 4 |
| DENv234 | 108 | 31 | 119 | – | 108 | 109 | 109 | 2 |
| DENv1234 | 108 | 31 | 109 | $< 1$ | 108 | 147 | 108 | 10 |

vaccination should take place according to this constraint for a constant and an age-dependent efficacy respectively. Additionally the increase of the lifetime expected risk from the minimum that is caused by this constraint is given. Clearly the overall conclusion remains that vaccination should take place as close to the ideal age as possible. For all vaccination ages below 9 years this means the vaccine should be administered once individuals turn 9 years old. Again almost all optimal vaccination ages for CRS (b) lie within the permitted age-range both for a constant and an age-dependent efficacy. For an age-dependent efficacy this is also true in the other scenarios. The percentage increase whenever the vaccination age is outwith the permitted age-range is much lower in the case of lethality than in that of hospitalisation. For a constant vaccine efficacy the increase is between 17% and 147% in CRS (a) and CRS (c) and between less than 1% and 10% in CRS (b) and CRS (d). For an age-dependent efficacy the lifetime expected risk under the current restriction increases by no more than 12%.

Table 6.11: The vaccination age $A_1$ in months which lies within the permitted age-range for the vaccine and minimises the lifetime expected risk $E$ of lethality. The percentage increase from the optimal lifetime expected risk $\delta_E\%$ is given for any case in which the optimal vaccination age lies outwith the permitted age-range of Dengvaxia. For cases in which vaccination is not recommended the minimal lifetime expected risk is zero, so that the percentage increase is given by $\infty$. The vaccine efficacy is assumed serotype-specific and age-dependent as given in Table 1.1

| | CRS (a) | | CRS (b) | | CRS (c) | | CRS (d) | |
|---|---|---|---|---|---|---|---|---|
| | $A_1$ | $\delta_E\%$ | $A_1$ | $\delta_E\%$ | $A_1$ | $\delta_E\%$ | $A_1$ | $\delta_E\%$ |
| DENv1 | 108 | 1 | 538 | $\infty$ | 108 | – | 538 | $\infty$ |
| DENv2 | 108 | – | 538 | $\infty$ | 108 | – | 538 | $\infty$ |
| DENv3 | 108 | 4 | 119 | $\infty$ | 108 | – | 165 | $\infty$ |
| DENv4 | 108 | – | 109 | $\infty$ | 108 | – | 109 | $\infty$ |
| DENv12 | 108 | – | 212 | – | 108 | – | 109 | – |
| DENv13 | 108 | 2 | 165 | – | 108 | 1 | 109 | – |
| DENv14 | 108 | – | 168 | – | 108 | – | 109 | – |
| DENv23 | 108 | – | 159 | – | 108 | – | 109 | – |
| DENv24 | 108 | – | 159 | – | 108 | – | 109 | – |
| DENv34 | 108 | – | 109 | – | 108 | – | 109 | – |
| DENv123 | 108 | – | 135 | – | 108 | 7 | 109 | – |
| DENv124 | 108 | – | 139 | – | 108 | $< 1$ | 109 | – |
| DENv134 | 108 | – | 109 | – | 108 | 1 | 109 | – |
| DENv234 | 108 | – | 109 | – | 108 | – | 109 | – |
| DENv1234 | 108 | – | 109 | – | 108 | 12 | 108 | – |

Restricting the vaccination age to be above 9 years still has a negative effect in the case of lethality. The effect again highly depends on the CRS and is also very different for the specific serotype combinations. It may therefore indeed be best to revise this minimal age especially if it is solely based on the fact that the efficacy is higher in individuals aged 9 years and above since this may be due to the serostatus of the recipient rather than the age per se.

### 6.4.4 Summary for Endemic Regions with Four Serotypes

In most endemic regions of Brazil all four dengue serotypes coexist. This can therefore be considered the most likely scenario so that a summary of the results for such an endemic area will be given in the form of forest plots. The results for a constant vaccine efficacy and, where applicable, vaccine-induced risk are presented in Figure 6.14, while those for the age-dependent case are shown in Figure 6.15.

In both figures the optimal vaccination ages for all four CRSs are presented for each of the three considered risk functions. In addition to the optimal vaccination age an age-interval in which near-optimal vaccination is possible is marked as well. Note that near-optimal vaccination is defined in terms of an increase of no more than 5% from the minimal lifetime expected risk. These intervals can be understood as the uncertainty in the optimal vaccination age. Dengvaxia is only licensed for the use in individuals above the age of 9 years in Brazil. A line marking the minimal age according to this restriction is therefore included in the forest plots.

Begin by considering the age-independent case which is shown in Figure 6.14. Here it is clearly visible that the differences between the risk of hospitalisation and that of lethality are fairly limited. Considering the cut-off due to the step-death function this is to be expected. For both risk functions the optimal vaccination ages are very low with the exception of CRS (b) in which case the optimal vaccination age is close to or just above the minimal age for Dengvaxia. Interestingly this is also the CRS with the largest interval in which near-optimal vaccination is possible. CRS (a) and CRS (c), where primary infections are assumed risky, seem to have the least uncertainty, i.e. the smallest ranges in which near-optimal vaccination is possible. For a vaccine-induced risk this is not the case. The largest uncertainty in this scenario is obtained for CRS (c). The scenarios CRS (c) and CRS (d) which consider PCI, have the largest age-ranges for near optimal vaccination for this risk function. And the assumption of risky primary infections can have the opposite effect on the certainty than for the other two risk functions.

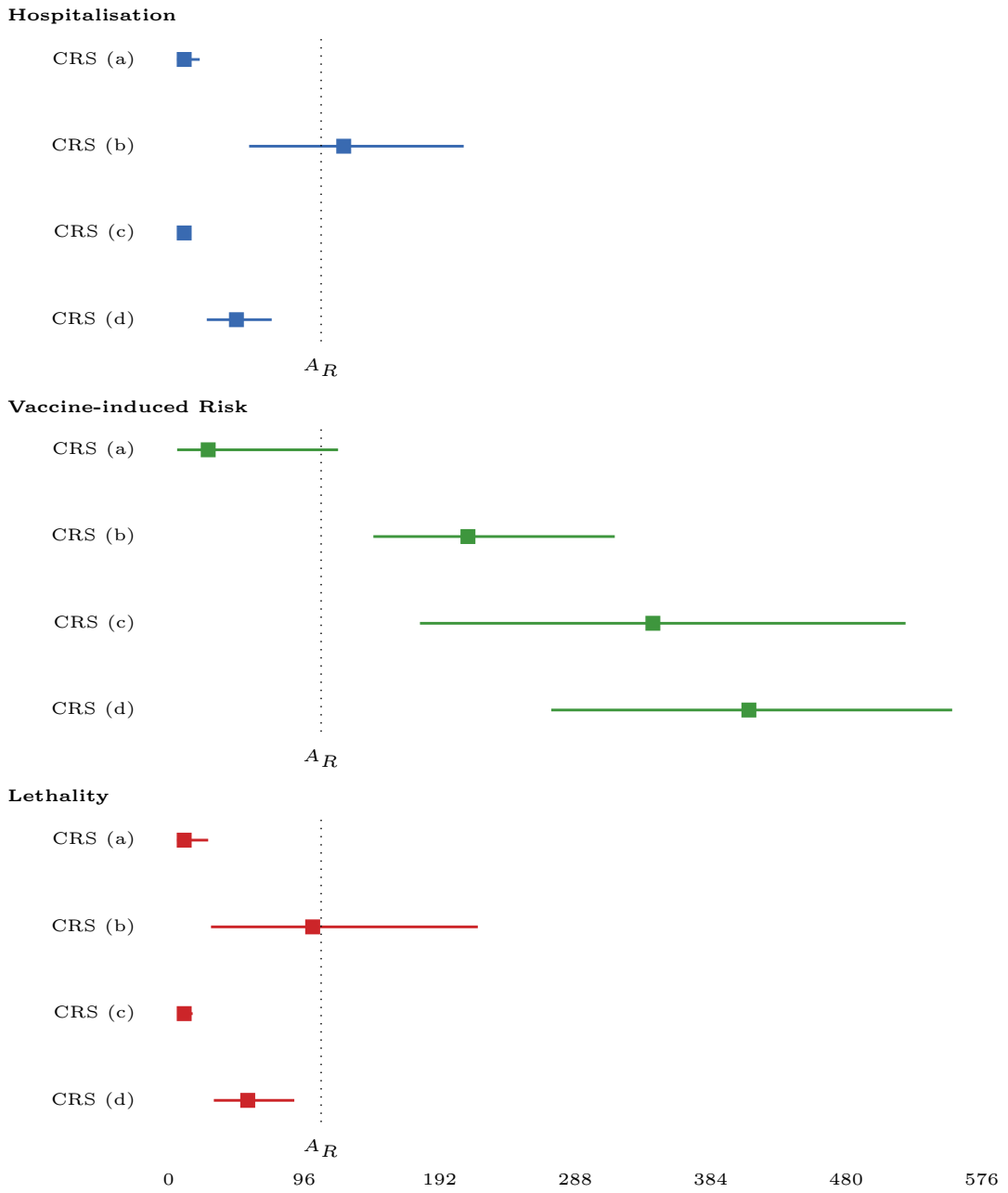



Figure 6.14: Forest plot for each scenario considering four coexisting serotypes with a constant vaccine efficacy. The squares mark the optimal vaccination age, while the horizontal lines indicate the interval in which the lifetime expected risk exceeds the minimum by no more than 5%. These intervals give an indication of the uncertainty in the optimal vaccination age. The vertical dotted line corresponds to the minimum age $A_R = 9$ years for vaccination according to current license restrictions.

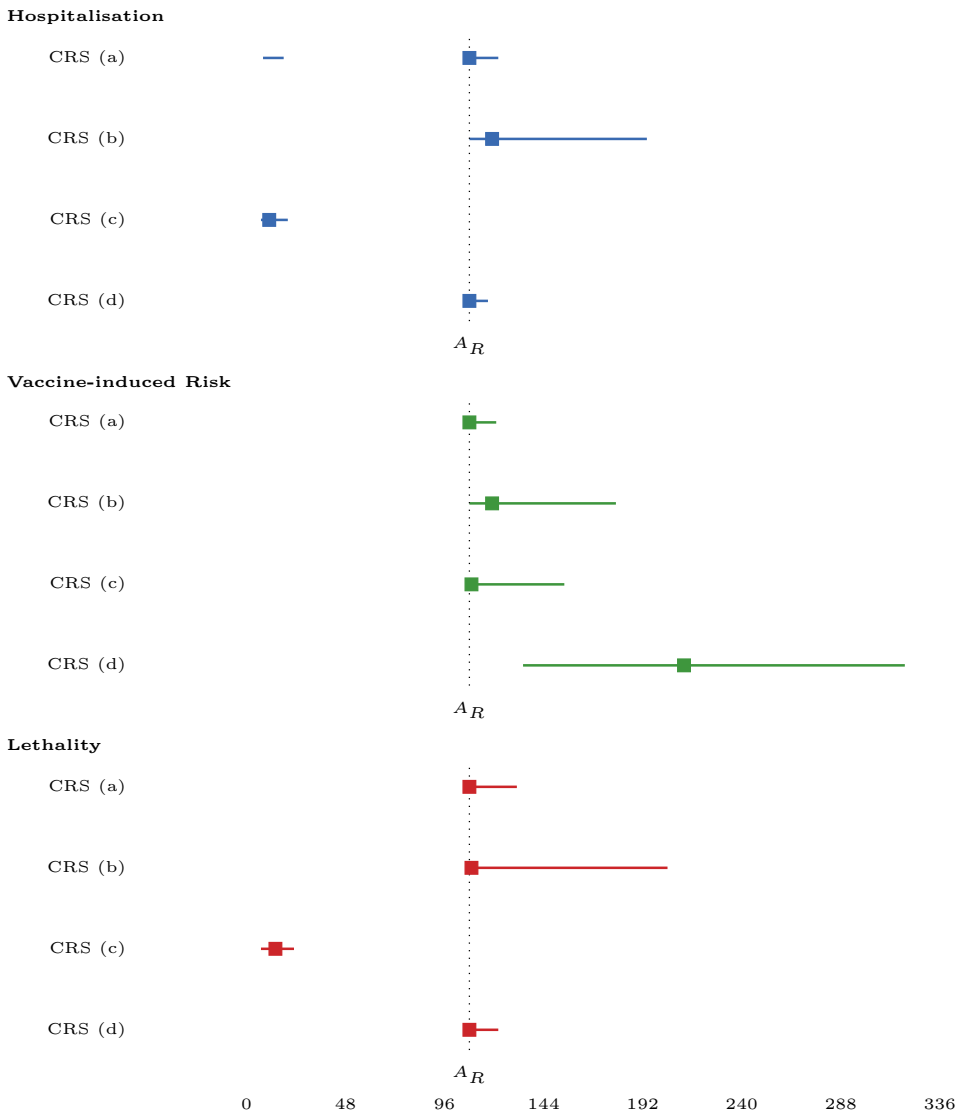



Figure 6.15: Forest plot for each scenario considering four coexisting serotypes with an age-dependent vaccine efficacy. The squares mark the optimal vaccination age, while the horizontal lines indicate the interval in which the lifetime expected risk exceeds the minimum by no more than 5%. For CRS (a) when the risk of hospitalisation is considered, two separate intervals in which the lifetime expected risk is at most 1.05 times as high as the minimum exist as shown by the discontinuous horizontal line. These intervals give an indication in the uncertainty of the optimal vaccination age. The vertical dotted line corresponds to the minimum age $A_R = 9$ years for vaccination according to current license restrictions.[1]

[1] In CRS (a) for the risk of hospitalisation the lifetime expected risk is close to its minimum in two distinct age intervals. It is first near optimal at around 12 months and increases again to above 1.05 times the optimum for some time. As soon as the vaccine has a higher efficacy at 108 months it reaches the minimal lifetime expected risk and then stays close to this risk for a short time. The abrupt increase in efficacy at 108 months is also responsible for the one sided interval around the optimal vaccination age in many of the other cases.

Considering that the vaccine-induced risk is likely due to ADE this should be expected. The large uncertainty for this risk function may be due to the fact that in the case of a vaccine-induced risk it is crucial to strike a balance between vaccinating too early and too late. On the one hand, when vaccinating too early many recipients will be seronegative and thus exposed to an increased risk later on. On the other hand, when vaccinating too late many infections will already have occurred and the vaccine will no longer have a significant effect (negative or positive).

From Figure 6.15 the large effect of the assumption of an age-dependent vaccine efficacy and age-dependent vaccine-induced risk can be seen. Firstly the optimal vaccination ages are now almost all above the minimal age for Dengvaxia. Secondly the uncertainty in optimal vaccination age is significantly reduced in almost all cases. This is due to the much lower efficacy in individuals under the age of 9 years, i.e. it is certainly better to wait a few months to vaccinate if the vaccine will then be much more effective. Again there is little difference between the risks of hospitalisation and lethality and indeed in general the observations regarding the uncertainty in optimal vaccination age for non vaccine-induced risk are similar. However, it is important to consider CRS (c) where the optimal vaccination age is still very low. Indeed this was already the scenario with the lowest optimal vaccination age in the constant vaccine efficacy case. In this case primary infections should be prevented by vaccination while post-secondary infections do not contribute to the risk. It is therefore best to vaccinate early even if the vaccine efficacy is somewhat lower. For a vaccine-induced risk the observations relating to the optimal vaccination age and decrease in uncertainty are similar to the other two risk functions. That is, due to the much higher efficacy and lower vaccine-induced risk, the age ranges in which near-optimal vaccination is possible in CRS (a), CRS (b) and CRS (c) are more restricted. In CRS (d) this is not the case since vaccination should ideally take place significantly after the age for which the vaccine efficacy increases and the risk decreases. It is therefore not particularly affected by this assumption. Note that in comparison to the previous chapter the assumption of an age-dependent vaccine-efficacy and vaccine-induced risk does, however, have a much larger effect overall. However, especially in light of the vaccine-induced risk function it needs to be noted that the high uncertainty makes it necessary to perform more analysis before a vaccination campaign can be based on the presented results.

## 6.5 Conclusions

In this chapter a single-serotype model as given and analysed in Chapter 3 was used to describe the transmission dynamics of dengue. The death rate in the human population was modelled by a step-death function which is a more realistic description of the dynamics in Brazil than a constant death rate. Serological data from the pre-vaccine era in Brazil was used to determine the overall force of infection at the pre-vaccine steady-state. Considering that the age-dependence of the force of infection is solely caused by the age-dependence of the rate at which mosquitoes bite humans the biting rate was then obtained from the relation $\lambda_0(a) = \xi_T q(a)$. The use of serological data as opposed to biting rate data resulted in a residual force of infection and thus a residual biting rate at higher ages. This has a large impact since it implies that infections can occur at any age even if children are most likely to be affected. Serological data therefore leads to a more realistic description of the transmission dynamics than the use of biting rate data since case report data shows that infections do indeed occur at any age [29].

Note that no serotype-specific serological profiles were available so that the overall serological profile was used together with the serotype-specific reported number of cases to estimate the steady-state force of infection before the introduction of a vaccine for each of the four serotypes. From these forces of infection the serotype-specific steady-state force of infection for a given vaccination strategy could be determined. Having obtained the force of infection for a specific vaccination strategy the lifetime expected risk of hospitalisation or lethality and thus the optimal vaccination age that minimises the corresponding risk could be computed.

As in the previous chapter the lifetime expected risk was used to incorporate cross-reactions between the different serotypes. These are not taken account of in the model since only a single-serotype is considered but are very important when determining the optimal vaccination age. In particular ADE and PCI after two heterologous infections are theories that are being discussed but not yet fully understood. ADE implies that primary infections are less risky or even completely risk-free. Infections become risky only once heterologous antibodies bind onto the infecting virus cells and facilitate the entrance into the viruses' target cells [73, 87]. Very few third and fourth infections are recorded so that it is assumed that two heterologous infections confer PCI [53, 54, 115] and post-secondary infections are therefore understood to be free of risk. The four CRSs that were studied are therefore based on risky or risk-free primary infections and symptomatic or asymptomatic tertiary and quaternary infections.

Another observation that still requires more research is the possibility that the vaccine induces a higher risk in some recipients. Initially the Dengvaxia trial results indicated that vaccination was beneficial for all trial participants. However, an increased risk particularly in young seronegative recipients was observed in the third year after the initial dose of the vaccine was administered [66]. The theory is that vaccine-induced antibodies can cause a higher virulence in subsequent infections effectively causing vaccine-induced ADE [3]. Based on the higher recorded proportion of hospitalisations in seronegative vaccine recipients compared to seronegative individuals who did not receive the vaccine the vaccine-induced risk of hospitalisation was incorporated and its effect on the optimal vaccination age analysed.

The Dengvaxia trials also indicated that both the efficacy of the vaccine and the risk it potentially induces are age-dependent. The efficacy was found to be higher in children above the age of 9 years while the increased risk in seronegatives was lower in this age group [32, 66, 132, 133]. However, it is being argued that age is merely a surrogate for serostatus with the vaccine performing better in older children simply because they are more likely to be seropositive [4]. More than that the trial analysis based on the age-groups of individuals below 9 years and 9 years or above is being challenged [38]. The lifetime expected risk was therefore initially computed for the risk of hospitalisation and the risk of lethality with a constant efficacy but the effect of the age-dependence was discussed and the results presented in both cases. Similarly for the risk of hospitalisation with a vaccine-induced risk the age-groups were initially disregarded both for the efficacy and the increased risk in seronegatives but then taken into account to determine the impact on the optimal vaccination age.

The age-related risk of hospitalisation and lethality displays very similar behaviour for young children and young to middle-aged individuals. For children a high risk both of hospitalisation and lethality has been recorded, while young adults and middle-aged individuals have a much lower risk. At older ages both the risk of hospitalisation and lethality increase. However, the risk of lethality at ages above 70 years is far higher than the risk of lethality for children. This is not the case if hospitalisation is considered. In the previous chapter there was no residual force of infection and therefore little chance of an infection at these high ages. With the residual term infections may still occur even at very high ages. However, the step-death function leads to a cut-off at the age of 73.8 years so that the very high risk later on will not be relevant or overestimated as it was with a constant death rate. Interestingly despite the residual force of infection

the difference between the optimal vaccination ages that are obtained for the two risk functions, assuming that antibodies from the vaccine have the same effect as those from natural infection, in the different CRSs are fairly small. In CRS (a) and CRS (d) the optimal vaccination ages are very low independently of the risk function. They are between 9 and 20 months for the risk of hospitalisation and between 9 and 23 months for the risk of lethality. The largest difference can be observed in CRS (b) where optimal vaccination ages are higher for the risk of hospitalisation by up to 116 months. In CRS (d) the vaccination ages are more similar but both increases and decreases are observed when lethality is considered instead of hospitalisation. Aside from these differences the trends that were observed for both risk functions are identical so that only the case of hospitalisation will be discussed in detail.

The most relevant factor in determining the optimal vaccination age was again the CRS as could be seen from Table 6.1. If primary infections are risky, i.e. in CRS (a) or CRS (c), the optimal vaccination ages are very low: between 9 and 20 months. However, in CRS (b) and CRS (d) where they are free of risk, the optimal vaccination ages are higher and vary much more. Clearly in both these scenarios vaccination is not recommended if there is only a single serotype since without vaccination the lifetime expected risk is zero. Due to primary infections not causing any risk it is not necessary to vaccinate early so that the optimal vaccination ages are much higher. In CRS (b) the optimal vaccination ages for several coexisting serotypes are between 124 and 335 months where the optimal vaccination age tends to decrease as the number of serotypes increases. In CRS (d) a similar observation regarding the number of serotypes can be made. The optimal vaccination ages are between 48 and 123 months in this case. The decrease in optimal vaccination age for a higher number of endemic serotypes is intuitive since the average age of infection decreases. If for example specifically a secondary infection should be targeted as in CRS (d) the age at which it occurs is lower so that vaccination needs to take place earlier. In the case of risky primary infections this cannot be observed since the vaccination ages are already very low to prevent primary infections and vaccinating any earlier will not be effective due to the persistence of maternal antibodies in infants. The fact that vaccination ages are lower in CRS (d) than in CRS (b) is due to PCI. Considering that third and fourth infections are risk-free if there is PCI vaccination will not be beneficial if it can only prevent these types of infection. It therefore needs to take place ideally between the primary and secondary infection in CRS (d). In CRS (b) any prevented post-primary infections will reduce the risk so that if many third and

fourth infections can be prevented a higher vaccination age will still reduce the lifetime expected risk.

Apart from the CRS the efficacy and force of infection influences the lifetime expected risk of hospitalisation. This became clear by considering a single endemic serotype as was shown in Figure 6.3. The high force of infection and low efficacy for DENv1 means that this serotype causes the highest risk independently of vaccination age. The high efficacy for DENv3 and DENv4 on the other hand means that if vaccination takes place at an age at which many infections have yet to take place the risk can be significantly reduced. For DENv2 the low efficacy on the other hand indicates the benefit of vaccinating is limited. These observations are similar when the vaccine efficacy is taken to be age-dependent. However, the assumption of an age-dependent efficacy has a large impact on the optimal vaccination age. In CRS (d) for several coexisting serotypes vaccination should take place at 108 or 109 months. Due to the higher efficacy in individuals over the age of 9 years compared to the pooled efficacy some optimal vaccination ages in CRS (b) slightly decrease as more infections can be prevented. In CRS (a) and CRS (c) the optimal vaccination ages are mainly influenced if DENv4 is endemic since the difference in efficacy between the two age-groups is largest for this serotype.

In CRS (b) and CRS (d) many of the optimal vaccination ages are within the permitted age-range of 9 to 45 years or very close to 9 years. However, in CRS (a) and CRS (c) the optimal vaccination ages are much too low for the current licence. Restricting the vaccination ages leads to a significantly worse outcome in these CRSs. Vaccination should take place as close to the ideal age as possible, i.e. at 9 years. The increase from the minimal lifetime expected risk that can be achieved through vaccination is up to 223%. In general the increase is higher in CRS (c) than in CRS (a). If primary infections are indeed risky it might be particularly necessary to reconsider the licence restriction. For risk-free primary infection only very few optimal vaccination ages are below the minimal vaccination age and those are often very close to 9 years so that the percentage increase is very small. With an age-dependent efficacy the licence restriction has less effect since more ages are at or above the minimum age of 9 years. In fact, independently of the considered CRS, the lifetime expected risk increases by no more than 39%.

A higher proportion of hospitalisations in seronegative vaccine recipients compared to seronegative trial participants that were in the control group indicates that Dengvaxia increases the risk in subsequent infections for these recipients. This higher relative risk eventually led to a revision of the WHO guidelines re-

garding to use of Dengvaxia [132, 133]. Based on this increased relative risk the lifetime expected risk of hospitalisation with a vaccine-induced risk was considered in order to determine whether vaccination should still be carried out if it can be harmful to some individuals and if so at which age it should be administered.

From Tables 6.5 and 6.6 for a constant and an age-dependent efficacy and vaccine-induced risk respectively it became clear that in most cases vaccination is indeed still recommended. Clearly if there is only a single serotype in existence and primary infections are risk-free vaccination should not be carried out independently of whether the vaccine induces a risk or not. When the age-groups of the vaccine trials are disregarded vaccination is, however, no longer recommended if only DENv1 or DENv2 is endemic in CRS (c) as well as if DENv2 coexists with either DENv3 or DENv4 in CRS (d). Additionally many optimal vaccination ages in CRS (b), CRS (c) and CRS (d) are much higher than without the vaccine-induced risk. This is due to the fact that even if primary infections are risky they should not be targeted since successfully vaccinating seronegatives against non-endemic serotypes or only some endemic serotypes will increase the risk the individual experiences in a breakthrough infection. It is therefore better to vaccinate only once the majority of individuals have had at least one infection and are thus seropositive. The optimal vaccination ages in general still decrease with an increasing number of serotypes as was observed without the vaccine-induced risk since again the average age of infection decreases. For risk-free primary infections the optimal vaccination ages are particularly high. The risk increases when seronegatives are vaccinated and the shape of the risk function is a very flat function of the vaccination age so that even the optimal vaccination age does not reduce the risk significantly. For risky primary infections a balance between increasing the risk in some recipients but preventing as many infections as possible is reached at earlier vaccination ages. In fact, if all infections are risky as is the case in CRS (a) the optimal vaccination ages are often still very low. In this case vaccinating early can clearly still reduce the risk. However, from Figures 6.8 to 6.11 it can be seen that in general for CRS (a) the lifetime expected risk increases more rapidly as a function of vaccination age compared to the other CRSs.

If the age-groups of the trials are taken account of with respect to the vaccine efficacy and the increased risk in seronegatives the results are slightly different. Only very low vaccination ages in CRS (a) and CRS (c) are vastly higher than without the vaccine-induced risk. Due to the decrease in risk at 9 years and the increase in efficacy this is to be expected especially since primary infections should no longer be targeted. In CRS (d) some vaccination ages are also much higher

with a vaccine-induced risk since vaccinating seronegatives will be harmful. It is better to only vaccinate very late to prevent vaccination of seropositives even if that means that vaccination will not have a large impact overall.

Restricting the vaccination ages in such a way that all three doses are administered to individuals aged 9 to 45 years has much less impact if the vaccine induces a risk. If the age-groups are disregarded the increase from the minimal lifetime expected risk is very small, i.e. and no higher than 46% for any CRS. If the age-groups of the vaccine trial are considered for the efficacy and vaccine-induced risk all optimal vaccination ages are within the permitted age-range. If Dengvaxia indeed performs differently depending on the age of the recipient and induces a higher risk in seronegative recipients the licence restriction can remain in place. However, in this case the newer recommendation of only vaccinating seropositives should be considered to reduce the risk of causing some individuals harm.

The vaccine-induced risk was again only considered for the risk of hospitalisation since so far there is no available data showing an increased risk in lethality. However, the trial cohort was small and the time-scale short so that it can be assumed that the risk of lethality in seronegatives will be influenced in a similar way. While the optimal vaccination ages for the risk of hospitalisation and lethality are similar without a vaccine-induced risk this is not necessarily the case if the vaccine-induces a higher risk in seronegatives. Based on the higher proportion of hospitalisations in some vaccine recipients vaccination campaigns should be carefully considered independently of the aim of vaccination.

In the previous two chapters the limitations due some of the key modelling assumptions were discussed. It was seen that both while the assumption of a constant biting rate was unrealistic, assuming an age-dependent biting rate which was derived from biting rate data was also problematic. In this chapter it was therefore assumed that the biting rate was age-dependent. However, instead of deriving it from biting rate data it was indirectly derived from the proportion of seropositives in Brazil. Compared to the biting rate data the serostatus data certainly leads to a much better representation of the biting behaviour in Brazil. However, what it does represent is an average over Brazil. Considering that Brazil is a large country spanning different climate zones and with a large divergence in population density both of humans and mosquitoes such an average cannot be used to determine the optimal vaccination age across Brazil. Indeed the analysis presented in this thesis should be carried out at a much smaller scale with parameters that closely represent the local or at least regional conditions of dengue

transmission. It is for example likely that the optimal vaccination age in regions with a much lower force of infection (and therefore level of seropositivity in the population) would require vaccination at later ages in all considered scenarios. In contrast some densely populated areas such as slums in the mega-cities of the country may have a much higher level of seropositivity especially if the conditions for a large mosquito population are given. In such areas vaccination should potentially target even younger age groups than the results in this chapter would suggest. However, the results can be seen as a guidance and the modelling framework can be used to carry out the analysis with more adequate parameters for a target region.

Another key assumption in this chapter was the vaccine-induced risk. The limitations of this assumptions have already been discussed in the previous chapter. To summarise the risk is based on only a small trial cohort and it remains unclear whether the risk is a long-term or short-term effect. Consequently the results may be misleading and the model should be re-analysed once more and more accurate data becomes available.

Similarly to the previous chapter the results demonstrate that effect of a vaccine-induced risk is significant. Particularly if the vaccine efficacy is actually age-independent it is very important to determine whether the vaccine does or does not induce a risk in seronegatives. Additionally more research needs to be carried out to determine which CRS is most realistic since the optimal vaccination ages highly depend on the corresponding assumptions. This is the case independently of whether the vaccine induces a risk or not.

The model that was used in this chapter was very similar to that in the previous chapter. In both cases the human population was modelled with a step-death function to increase the accuracy of the predicted optimal vaccination ages. A step-death function is more realistic for Brazil than the commonly used simplification of a constant death rate. The main difference to the model in the previous chapter was that the biting rate and thus the force of infection had a residual term and did not tend to zero at older ages. This residual term was obtained by considering the serological profile of Brazil before the introduction of a vaccine to determine the steady-state force of infection and the biting rate. The benefit of the serological profile compared to the biting rate data that was used in the previous chapter is that serological data is much more reliable. Mosquito populations are not only seasonal but also very different across different areas and the counting of bites is difficult. The serological profile can be obtained through more reliable blood tests. However, the serological profile that was available for

Brazil is not serotype-specific. This is a shortfall in the data that was used. It would improve the accuracy of the results drastically if serotype-specific forces of infection could be derived from such data as opposed to estimated through the use of case report data. Now that Dengvaxia has been introduced in Brazil the collection of such profiles is no longer possible and only the post-vaccine profile could be obtained. This serological profile would be impacted by vaccination so that the mosquito biting rate could not be obtained easily from such data. With the available serological data the estimates that were presented in this chapter can therefore not be improved without adapting the model itself. However, even though the obtained optimal vaccination ages are not precise they can certainly be used as a guideline. Before a vaccination campaign can be started it is therefore most crucial to identify the most realistic CRS and the endemic serotypes in the targeted region. Additionally the Dengvaxia trial data needs to be carefully evaluated to determine whether the vaccine performance is impacted by the age of the recipient.

Chapter 7

# Conclusions and Future Work

## 7.1 Introduction

Dengue is endemic in over 120 countries in which an estimated 390 million dengue infections occur every year [22, 23]. Roughly 25% of these infections are symptomatic with some infections having a severe or even fatal outcome [22]. Brazil is one of the most affected countries with approximately five million apparent infections annually [22] and in the future it can be expected that even more infections will be recorded since the incidence of dengue has been on the rise globally and in Brazil for decades [15, 166]. There is also some risk in non-endemic countries as it is not uncommon for travellers to return from endemic regions infected with the virus [162, 165]. In recent years some of these imported cases led to autochthonous dengue infections in countries like France and Croatia [125, 141, 149] highlighting the risk of the virus spreading further and affecting an ever larger proportion of the world's population.

Considering the spread and incidence of dengue it is not surprising that the virus poses a significant burden on the health care systems of many tropical and sub-tropical countries. However, there is a high uncertainty of the real burden in some regions, particularly the burden on the Brazilian health care system is unclear [22]. There are several reasons for this uncertainty. One of the main reasons is that symptoms, particularly at the beginning of an infection, are extremely similar to those of other febrile illnesses so that misdiagnosis is very common. Additionally infections are significantly under-reported since many individuals undergo asymptomatic infections and even those that do experience symptoms such as a high fever, pain and rashes do not always seek medical attention. In light of the recent introduction of the first vaccine against dengue it is, however, very important to assess possible large scale vaccination campaigns with respect

to how effectively they are able to ease the burden on affected health care systems. The aim of this thesis was to determine the vaccination age which most significantly reduces the risk of severe dengue infections with the recently licensed dengue vaccine Dengvaxia in Brazil. However, a number of different model assumptions and assumptions relating to the vaccine itself led to a multitude of optimal vaccination ages which will be discussed in this chapter. Subsequently it will also be highlighted which questions remained unanswered and in which direction the work can be continued to assist health care authorities in making the best decisions for large scale vaccination campaigns.

## 7.2 Conclusions

In this thesis mathematical modelling techniques were used to determine the optimal vaccination age for dengue in Brazil with the recently licensed vaccine Dengvaxia. The optimal vaccination age was defined in such a way that the burden on the population as a whole was minimised by a three-dose vaccination schedule according to a routine vaccination calendar. Catch-up campaigns were not considered since booster doses are not currently recommended.

It could be seen that many different factors influence the optimal vaccination age. Amongst them are the chosen risk function, the model assumptions, the conditions in the endemic regions, i.e. how many and which serotypes coexist, and the possible CRSs. Additionally some factors relating to the vaccine itself are decisive. The vaccine effectiveness and the potentially increased risk vaccination may cause in seronegative recipients have a significant impact on the optimal vaccination age. Restricting the vaccination age to between 9 and 45 years according to the current licence also influences the outcome of the vaccination campaign. All of these factors will be discussed in this section. However, in general the combination of all factors is relevant so that only the overall trend for any specific assumption can be pointed out. The limitations of the presented results are also be discussed with a particular focus on the data that was used to determine the optimal age to vaccinate against dengue in Brazil.

### 7.2.1 Chosen Risk Function

The burden on the health care system will most effectively be reduced by minimising the risk of severe dengue rather than that of any disease severity. This is due to many infections being asymptomatic or very mild so that the health care system is mostly affected by individuals experiencing DHF and DSS, i.e. severe

dengue infections. In Section 3.3 the burden on the society was defined based on the lifetime expected risk where the risk of requiring hospital treatment or dying due to an infection was considered. Both risk functions were determined from age-dependent pre-vaccine data collected through SINAN and can be understood as surrogate risk functions for the risk of severe dengue.

There are many similarities between these two risk functions such as a peak in risk at fairly young ages, i.e. at 5.5 years for the risk of hospitalisation and at 4 years for the risk of lethality, and an increase in risk in older individuals. However, for lethality the risk at older ages far outweighs the risk in children. This is not the case for the risk of hospitalisation where the risk at very high ages is fairly similar to that for children. Intuitively one might therefore expect a higher optimal vaccination age for the risk of lethality but no clear overall trend could be observed across all considered scenarios. However, depending on the considered model assumptions which risk function was chosen did not always impact the optimal vaccination age significantly as will be discussed in the following subsection.

### 7.2.2 Model Assumptions

Initially a simplified model with a constant human death rate and a constant mosquito biting rate was assumed. This model was then improved by using a more realistic step-death function and an age-dependent rate at which mosquitoes bite humans. The age-dependent biting rate was determined from biting rate data and was then used to compute the force of infection. Subsequently, to further enhance the accuracy of the predicted optimal vaccination age, serological data was used to determine the pre-vaccine force of infection and thus the biting rate and the force of infection after the initiation of a vaccination campaign. Serological data is less prone to errors than biting rate data since biting data is difficult to collect and significantly varies on a spatial-temporal scale.

The different model assumptions had a significant impact on the lifetime expected risk and the optimal vaccination age. The constant biting rate and constant human death rate that were used in Chapter 4 resulted in a lifetime expected risk that could be influenced at least to some degree at any vaccination age since even at very high ages there remained a chance of being infected under these assumptions. Consequently the optimal vaccination ages for the risk of lethality, which is particularly high at older ages, were very high so as not to increase the average age of infection to ages with more risk. For the risk of hospitalisation much lower optimal vaccination ages were obtained due to the risk being more

significant in children than in old individuals.

On the other hand, the age-dependent biting rate that was obtained from biting rate data in Chapter 5 resulted in a force of infection that tended to zero even at fairly young ages. Together with the step-death function that corresponds to a cut-off at the expected lifetime of humans this led to older individuals experiencing a very low risk of becoming infected. The lifetime expected risk was therefore not significantly impacted by vaccination above a certain age when these model assumptions were considered. The differences between the two risk functions were therefore almost negligible and the optimal vaccination ages were found to be comparably low for both risk functions.

When serological data was used to obtain the biting rate and thus the force of infection in Chapter 6 a force of infection with a residual term at older ages was found to be a more accurate fit than that obtained from the biting rate data in Chapter 5. Effectively this constitutes a combination of the previous two biting rate functions with a large force of infection at younger ages and some constant force of infection for older individuals. Vaccination therefore again impacted the lifetime expected risk to some degree at any age. However, due to the step-death function and the associated cut-off the two risk functions again led to similarly low optimal vaccination ages.

When comparing the results obtained in Chapters 4 to 6 there are two points that should be kept in mind. Firstly, a constant human death rate is a commonly used approximation in epidemiological modelling. However, a step-death function, while still a simplification, more accurately describes the real population dynamics. Secondly, considering that dengue infections have been recorded in individuals of any age but that the frequency of infections is highest in young children [29], it is clearly relevant to determine the age-dependence of the rate at which mosquitoes bite humans. A constant biting rate as used in Chapter 4 or an age-dependent one without a residual term such as that obtained from biting rate data in Chapter 5 can give some initial indication of the optimal vaccination age. However, it can be argued that the age-dependent biting rate with a residual term that was obtained from serological data in Chapter 6 leads to a more accurate representation of the actual biting rate and force of infection of dengue in Brazil. The results presented in Chapter 6 are therefore most reliable.

### Vaccination Mode

In this thesis the effect of vaccination was included by assuming that vaccination is completely successful with a probability corresponding to the vaccine

efficacy for each vaccinated individual. Consequently for a vaccine efficacy $\epsilon$ a proportion $\epsilon$ of the vaccinated population is modelled as completely protected against the corresponding serotype while the remaining individuals do not experience any effect due to the vaccine. This is a fairly common way of modelling the effect of vaccination. However, it would also be possible to consider that the entire vaccinated population experiences a level of protection $\epsilon$. In this case if an individual comes into contact with a serotype they were vaccinated against their probability of getting infected would be $1 - \epsilon$. Similar to many other vaccination models for dengue it was assumed that a successful vaccination corresponds to a silent natural infection. Such a silent infection was in some cases assumed to prime individuals to a higher risk depending on the considered CRS and whether vaccine-induced risk was considered or not. Particularly CRS (b) without a vaccine-induced risk is relevant in this case since this scenario most closely resembles the commonly used modelling assumptions of the wider research into dengue vaccinations [132].

### Individual versus Population Perspective

Further the effect of vaccination was evaluated at a population level. The optimal vaccination ages presented in this thesis thus maximise the overall benefit due to vaccination for the population. However, what was not specifically considered was the benefit or risk for each individual of the population separately. In light of the safety concerns and the fact that an induced risk due to vaccination may be highly correlated with the serostatus and not just the age of a recipient very different results may have been obtained if the individual perspective had been considered. In particular it is to be expected that under such considerations recommendations for seronegative and seropositive individuals would be different. Considering for example that vaccination may only be beneficial to seropositives the optimal age might be difficult to predict at a population level. It may in this case only be possible to predict a reasonable age at which the serostatus of a potential recipient should be confirmed. Then it would be possible to vaccinate only those individuals determined to be seropositive. By analysing the vaccine from an individual perspective it could also be possible to reduce the overall lifetime expected risk further especially in the case of vaccine-induced risk. In this case one would not induce any risk in some part of the population to achieve an overall benefit. Indeed, from an ethical point of view the population level analysis is questionable since it should not be acceptable to expose some vaccine recipients to a higher risk in order to decrease the overall risk. Considering the possibility

of the effect of vaccination depending on the serostatus of the recipient and the ethical shortcomings of a population level approach, it is important to keep in mind that the results presented in this thesis are merely a first approximation. More work remains to be done especially for the case of vaccine-induced risk.

### 7.2.3 Number and Combination of Serotypes

In Brazil all four dengue virus serotypes coexist since the reintroduction of DENv4 in 2010, however, not all four serotypes coexist at the same time in each endemic area [48, 114]. Considering that the vaccination age was found to depend on the number of coexisting serotypes as well as the specific combination of serotypes throughout Chapters 4 to 6 it is important to determine the situation in each endemic region before the introduction of a large-scale vaccination campaign.

The vaccine efficacies of the endemic serotypes, as well as their forces of infection were decisive for the optimal vaccination age. A higher efficacy indicates that more infections can be prevented particularly if vaccination is carried out an age at which most infections have yet to occur. However, vaccination while maternal antibodies persist is often unsuccessful and a balance needs to be found between vaccinating too early when many individuals will still be protected by maternal antibodies and vaccinating too late when many infections have already occurred. With respect to this the average age of infection is very important. A higher force of infection generally corresponds to a lower average age of infection and in order to reduce the risk and prevent natural infections the vaccination age will often be lower the higher the force of infection of the endemic serotypes is. In many, albeit not all, considered scenarios a higher number of serotypes therefore resulted in a lower optimal vaccination age since the overall force of infection increases with every additional serotype. However, vaccination campaigns lead to a shift in the average age of infection which can in some cases result in a higher lifetime expected risk if the age is shifted unfavourably. In fact vaccination is not always beneficial for any number of serotypes, e.g. if there is only a single endemic serotype the most important factor that determines if vaccination should take place is whether there is ADE or not. In fact, the considered CRS in general significantly influences the optimal vaccination age for any number and combination of serotypes.

In relation to the number and combination of serotypes it is also important to keep in mind that the effective reproduction numbers for each of the serotypes are an important factor in the observed differences. However, the exact values

of the effective reproduction numbers that were derived in Sections 4.3 and 5.3 are highly sensitive to the chosen start of the epidemic. Therefore a number of simulations were carried out with several different effective reproduction numbers which were omitted in the results sections of the corresponding chapters. In short this sensitivity analysis indicated that the optimal vaccination age and minimal lifetime expected risk does indeed depend on the effective reproduction number as one would expect. In fact it was seen that in general a higher effective reproduction number resulted in a lower optimal vaccination age and vice versa. This is in line with expectations since the effective reproduction number is closely related to the average age of infection, i.e. the higher the effective reproduction number the lower the average age of infection. In order to prevent a significant amount of infections vaccination needs to take place before the average age of infection. In the case of a vaccine-induced risk such generalisations could not always be observed due to the complicated balance that needs to be reached between not causing an increased risk in some vaccine recipients and achieving an overall benefit.

### 7.2.4 Cross-Reaction Scenarios

Of the 390 million estimated annual infections only roughly 100 million are symptomatic and many of these are fairly mild [22]. However, some infections are accompanied by severe plasma leakage, bleeding and organ failure. The reason for certain infections leading to such severe symptoms while others are completely asymptomatic is not yet fully understood despite the ongoing research into the different aspects of dengue transmission and antibody reactions. There are several theories regarding this phenomenon. The two most commonly accepted theories are ADE and PCI after two heterologous infections. ADE is based on the observation that the vast majority of severe dengue cases are secondary infections or infections in young infants with some level of maternal antibodies [73, 84, 93]. Third and fourth infections are not usually recorded and it is therefore assumed that two heterologous infections confer PCI against the remaining serotypes [53, 54, 115]. However, neither of these assumptions has been conclusively proven so far. The optimal vaccination age for the different model assumptions was therefore determined for each of the four possible CRSs based on ADE and PCI (cf. Section 3.4).

Recall that in CRS (a) all infections are considered risky, in CRS (b) all but primary infections are considered risky, in CRS (c) only primary and secondary infections are considered risky and in CRS (d) only secondary infections are con-

sidered risky. It is not surprising that these assumptions have a significant impact on the optimal vaccination age. In CRS (a) and CRS (c) primary infections need to be targeted in order to effectively reduce the risk for the population. On the other hand, in CRS (b) and CRS (d) it is not necessary to prevent primary infections since they are risk-free so that it is better to delay the vaccination until it is certain that maternal antibodies no longer persist. However, in CRS (c) and CRS (d) it is also important to vaccinate before most secondary infections occurred since vaccination after the secondary infection will no longer have any effect due to PCI. Consequently it could be observed that in general the optimal vaccination ages that were obtained in CRS (a) and CRS (c) are much lower than in CRS (b) or CRS (d). Additionally the optimal vaccination ages obtained for CRS (c) and CRS (d) tended to be lower than those for CRS (a) and CRS (b) respectively to ensure that fewer individuals with two prior infections are being vaccinated.

A further observation related to ADE was that if only a single serotype is endemic and primary infections were assumed risk-free, i.e. in CRS (b) and CRS (d), vaccination was not recommended at all. This can in fact be intuitively expected since in the absence of a vaccination campaign all natural infections will be risk-free primary infections. However, once vaccination takes place some infections will be secondary, tertiary or quaternary infections depending on how many serotypes an individual was successfully vaccinated against. This is due to Dengvaxia being an imperfect vaccine, i.e. it is not 100% effective, so that some recipients will be partially immunised and thus exposed to a risk in a possible subsequent natural infection.

The CRS was, in fact, one of the most decisive aspects for the optimal vaccination age. Considering the vastly different optimal vaccination ages that were obtained for the different CRSs it is therefore highly important to determine which of these scenarios is most realistic. Additionally ADE and PCI may have an effect on the transmission dynamics of the different serotypes which would indicate that more understanding of these cross-reactions will be beneficial not only for the determination of the ideal vaccination strategy but also for the understanding of the disease itself.

### 7.2.5 Age-Dependence of the Vaccine Efficacy

In addition to the uncertainties regarding antibody cross-reactions there is also some ambiguity relating to Dengvaxia and its ability to prevent severe dengue infections. In particular vaccine trials showed that depending on the age of the

recipient vaccination will have a different effect, i.e. it will be more effective in children above the age of 9 years than below this age [32, 66]. However, it has been argued that the analysis based on these age-groups is flawed [38] and some researchers maintain the position that age is merely a surrogate for the serostatus of the recipient with a higher efficacy in seropositive individuals [4, 5]. Therefore both a constant and an age-dependent efficacy were considered throughout this thesis.

Considering that the age-dependent vaccine efficacy for individuals below the age of 9 years is significantly lower than the age-independent vaccine efficacy but increases drastically once the vaccine is given to individuals above 9 years (cf. Table 1.1) it is not surprising that this assumption has a significant impact on the optimal vaccination age, particularly if the optimal vaccination age with a constant vaccine efficacy was found to be below the age of 9 years. In these cases an age-dependent efficacy often resulted in a much higher optimal vaccination age of 108 months, i.e. 9 years. However, even for cases in which the optimal vaccination age was above 9 years the age-dependence of the vaccine efficacy was found to be relevant. Due to the higher efficacy at ages above 9 years compared to the constant efficacy scenario more infections can be prevented. This resulted in lower optimal vaccination ages in some cases since the higher efficacy means that more infections can be prevented even at a slightly lower vaccination age.

The effect vaccination has on individuals of different ages is clearly highly relevant when determining the optimal vaccination age. However, it is unlikely that this type of step-function adequately describes the real behaviour of the vaccine. If the efficacy does indeed solely depend on the age of the recipient it is much more realistic that the efficacy increases continuously as the immune system develops and the response to the vaccine improves. So far it is still unclear whether the higher efficacy in older individuals is due to their age per se or whether it is higher because older individuals are more likely to have experienced a prior infection, i.e. the serostatus rather than the age of the recipient determines the efficacy. In fact, the serostatus of the recipients may be the most important factor for the outcome of a vaccination campaign as will be discussed in the following subsection.

### 7.2.6 Vaccine-Induced Risk

The most recent development regarding the effect of Dengvaxia is that an increased risk of requiring hospital treatment in subsequent natural infections has

been observed in some vaccine recipients [132]. Particularly young seronegative individuals seem to be vulnerable to experiencing severe symptoms due to vaccine-induced antibodies. After considerable pressure from the research community [3, 6, 74] the WHO therefore changed its recommendation from vaccinating any individuals above the age of 9 years to only vaccinating those above this age who have had a prior dengue infection [132, 133]. The manufacturer of Dengvaxia, Sanofi Pasteur, also revised their position and updated the label of the vaccine [135].

These are fairly recent developments so that the increased risk in seronegatives was only considered for the more advanced model with a step-death function for the human population and an age-dependent mosquito biting rate in Chapters 5 and 6. In fact, the vaccine-induced risk was only applied to the risk of hospitalisation since so far no increase in fatal infections has been observed for any vaccine recipients. However, considering the relatively short time-frame of the vaccine trials and the small trial cohort it is possible that in the future an increased lethality risk will be observed. In this case the lethality related data needs to be evaluated if and when it becomes available.

The vaccine-induced risk had a significant impact on the optimal vaccination ages. However, depending on the CRS and the model assumptions the effects differed. In Chapter 5 the optimal vaccination age compared to the cases without any vaccine-induced risk increased drastically particularly in CRS (c) and CRS (d). Further for only a single endemic serotype vaccination is often not recommended. This is due to the high risk of successfully vaccinating a seronegative individual against a non-endemic serotype but not against the endemic serotype particularly if the vaccine efficacy is low. If vaccination is only carried out once the natural infection occurred it has no effect and will therefore not reduce the overall risk. The vaccine efficacy in this case is very important. If the vaccine efficacy and vaccine-induced risk are assumed constant, vaccination was found to be recommended for DENv3 and DENv4 in CRS (a) due to the higher efficacy of these serotypes. With an age-dependent efficacy the efficacy above 9 years is higher compared to the constant efficacy case for all serotypes and indeed vaccination was found to be recommended as long as primary infections are risky, i.e. in CRS (a) and CRS (c). For several coexisting serotypes the optimal vaccination ages for CRS (b) were higher than those for CRS (a), while those for CRS (c) and CRS (d) were found to be very similar. The vaccine-induced risk implies that it is harmful to vaccine seronegative recipients. However, in CRS (a) all infections are risky so that as long as sufficient individuals are successfully vaccinated against the endemic serotypes

vaccinating some seronegatives can be risked. If primary infections are risk-free vaccinating seronegatives is not only unnecessary but counter-productive so that the optimal vaccination ages for CRS (b) were found to be much higher. Considering that there was no residual force of infection due to the model assumptions and that due to PCI vaccination after a secondary infection does not have any effect CRS (c) and CRS (d) resulted in similar optimal vaccination ages.

In Chapter 6 the force of infection had a residual term. In this case the vaccine-induced risk resulted in much higher optimal vaccination ages compared to the risk of hospitalisation without such an increased risk in all CRSs apart from CRS (a). Again, the optimal vaccination ages for CRS (a) were not as impacted and remained fairly low. Due to the residual force of infection the optimal vaccination ages for CRS (c) and CRS (d) varied more than in Chapter 5.

With a vaccine-induced risk the ideal time to vaccine is after most primary but before many secondary infections have taken place. This is particularly true in CRS (c) and CRS (d) where successful vaccination of an individual who has had one prior infection against any other serotype will result in the individual no longer being at risk. However, independent of the model assumption and the considered CRS the lifetime expected risk was often a very flat function of the vaccination age. Therefore with a vaccine-induced risk the burden on the health care system cannot be reduced significantly even at the optimal vaccination age. Considering that large-scale vaccination campaigns are expensive it is therefore necessary to evaluate the benefits of such a campaign from a economic point of view if the recent concerns regarding the use of Dengvaxia in seronegative individuals prove accurate.

### 7.2.7 Vaccination Age under Licence Restrictions

The optimal vaccination age is influenced by many different factors as was discussed in the previous subsections. However, the current licence of Dengvaxia in Brazil in fact only permits the vaccine to be used in individuals between the ages of 9 and 45 years. This age-range was determined based on the age-dependent analysis of the vaccine trial data. Considering that the age-dependence of the efficacy and vaccine-induced risk are still being challenged this licence restriction may at some point have to be revised. For now the optimal vaccination age under the current age constraint needs to be known so as to most effectively decrease the burden on the Brazilian health care system. These ages were therefore determined for all model assumptions and CRSs and the effect of vaccinating at the ideal age

without any age-restriction was compared to the effect of vaccinating according to the current licence restriction.

The age-restriction results in vaccination being most beneficial as close to the optimal age as possible in almost all cases, i.e. for very low optimal vaccination ages vaccination should be carried out at 9 years and for very high optimal vaccination ages at 45 years. This is true independently of the risk function, model assumptions, number of serotypes, CRS and assumptions relating to the performance of the vaccine. However, the negative effect this restriction has on the lifetime expected risk and thus on the health care system clearly depends on other assumptions. In general many more of the determined optimal vaccination ages are already within the permitted age-range for an age-dependent efficacy (and age-dependent vaccine-induced risk) so that in this case the restriction has less impact. The percentage increase of the lifetime expected risk from its minimum is fairly low in this case even if the optimal vaccination ages are outwith the permitted age-range. This is particularly true for the model assumptions in Chapters 4 and 6 where the increase is no higher than 40% for an age-dependent efficacy. For a constant efficacy the maximum percentage increase is 223% for the risk of hospitalisation and lethality and 46% for the risk of hospitalisation with a vaccine-induced risk. In Chapter 5 the increase in general is much higher independent of the considered risk. However, again the increase with a vaccine-induced risk is much lower than if no vaccine-induced risk is considered. This is to be expected since the lifetime expected risk in this case is a very flat function of the vaccination age so that limiting the vaccination age has less effect.

For almost all combinations of factors that affect the optimal vaccination age the restriction of the age has a negative impact but this impact varies significantly. However, if it turns out that the age-group analysis of the vaccine trial data which resulted in this licence restriction is indeed flawed as some researchers claim [38] it is possible that the licence will be revised. Considering that many optimal vaccination ages did not conform to the permitted age-range this may in fact be necessary to ensure the greatest possible relief of the strain dengue puts on the Brazilian health care system.

### 7.2.8 Dengue Data and its Limitations

The results presented within this thesis are clearly subject to a large degree of uncertainty. Some of this uncertainty arises due to the modelling framework being an approximation of the real dynamics. However, more importantly the

lack of understanding of the dynamics, especially when it comes to the considered CRSs, inevitably results in a wide variety of optimal vaccination ages. This issue is closely related to the available data concerning the dengue viruses and the Dengvaxia vaccine. In the absence of more accurate data it is important to keep in mind that the results can only be understood as an indication of the optimal vaccination age. This is due to a number of limitations relating to the used data. Two of the most important limitations are the heterogeneity of dengue epidemiology and the fact that the vaccine trial data was extrapolated to ages far beyond the maximum recorded age.

### Heterogeneity of Dengue Epidemiology

Dengue is endemic in most of the subtropics and tropics. However, as discussed in Section 1.2.2 the different areas of the world are subjected to very different levels of transmission and thus experience the burden caused by the disease to a varying degree. The same is indeed true at a smaller scale. In Brazil some regions are much more affected by the virus than others. This is not surprising considering that Brazil spans several climate zones. But even within one city the transmission rates can differ significantly. This spatial heterogeneity can be due to a number of reasons. It is for example possible that in one neighbourhood the mosquito density is lower due to a successful implementation of preventive methods. On the other hand proximity to water reservoirs might result in more favourable conditions for the mosquito population. Similarly the transmission rate might be higher in a more densely populated neighbourhood especially if other factors contribute as well, such as a lack of air conditioning or more time spent outside at peak feeding times of the *Aedes aegypti*.

The spatial heterogeneity has a large impact on the optimal vaccination strategy. The higher the transmission rate the earlier vaccination should potentially be carried out. It was, however, neglected for the analysis carried out in this thesis. This is partly due to a lack of location specific data. The results therefore need to be understood to give an indication for the optimal vaccination age only. If the epidemiological situation in a region is similar to the average situation in Brazil the results are most realistic. However, as pointed out previously if the presented modelling framework is to be used to aid with the implementation of a vaccination campaign for a specific area it would be best to repeat the analysis with location specific data.

Indeed the transmission of dengue is not only location specific but also highly seasonal with a peak in transmission during the rainy season. In addition to this

it has been noted that the different dengue serotypes tend to replace each other as the most prevalent type in a multi-annual cycle. Dengue transmission therefore displays a highly spatial-temporal heterogeneity.

The seasonality may not be such a relevant factor when it comes to the optimal vaccination age. However, this should be confirmed by including a seasonal factor in the model. What will definitely have an impact on the results, however, is the prevalence of the epidemic serotypes. The results indicate that the vaccination age is dependent on the specific serotypes in circulation. Especially in light of the different theories regarding the serotype interactions it is therefore likely that the optimal vaccination age would also be impacted by such a temporal heterogeneity. It needs to be reiterated that the presented results only give a first indication and more analysis as well as collection of dengue epidemiological data is necessary to be able to make reliable suggestions for vaccination campaigns. Indeed it is also necessary to obtain more data relating to the vaccine itself since the data that was used has its limitations as will now be discussed.

**Extrapolation of the Vaccine Trial Data**

Independent of the specific model assumptions the trial data relating to the vaccine efficacy and the relative risk for vaccinated individuals as presented in Tables 1.1 and 1.2 were extrapolated to ages below and above the ages which were recorded in the vaccine trials. This has an effect on all results presented in this thesis independent of whether an age-dependent vaccine efficacy or a constant vaccine efficacy was assumed and whether vaccine-induced risk was considered or not.

Extrapolating the data to ages below 2 years can be justified by considering that the extrapolation is fairly limited towards birth. Even so it needs to be kept in mind that this is a strong assumption since infants may indeed have a much weaker immune response due to their not completely developed immune system. However, the model takes account of a reduced rate of seroconversion in infants based on the existence of maternal antibodies which mitigates this effect somewhat.

The extrapolation to ages above 16 years is a more precarious assumption. This is mainly due to the large age-range for which the extrapolation takes place. Data is only available for a fairly limited age-range between 2 and 16 years. However, it is assumed that the efficacy and relative risk at ages far above 16 years does not change. Considering that there is some evidence that both the efficacy and the vaccine-induced risk may indeed be age-dependent, it could be argued

that for adults the efficacy of the vaccine is likely to increase while the vaccine-induced risk is likely to decline. At very old ages a weaker immune system might conversely lead to a lower efficacy and higher vaccine-induced risk. Considering that the results rarely required vaccination at very high ages even with the probably overestimated benefits of the vaccine for these ages the extrapolation to these ages is less relevant. However, the true efficacy and vaccine-induced risk for young adults to middle-aged individuals could lead to a different outcome. For a higher vaccine efficacy this can be derived from the age-dependent vaccine efficacy results compared to the age-independent results throughout Chapters 4 to 6 where the increase in efficacy almost always led to a drop in lifetime expected risk. However, it is also important to keep in mind that the efficacy is not the only factor influencing the vaccination age. An important aspect is the average age of infection. If vaccination is to successfully prevent infections it needs to take place before most natural infections occurred, independent of whether the maximum efficacy has been reached. Seeing that dengue affects mostly young individuals it may therefore be argued that despite the underestimation of efficacy at higher ages the results presented within this thesis do serve as a first indication of when vaccination should take place. In either case the modelling framework presented in this thesis should be applied to a specific target region, ideally with more detailed data rather than taking the results as presented here.

Similarly the vaccine-induced risk may not play such a large role at older ages in which case it may be possible that vaccination could indeed be beneficial on a population level in some cases where it was determined not to be in this thesis. This is particularly important considering that the optimal vaccination ages when a vaccine-induced risk was considered was much higher than otherwise. Before a vaccination campaign, which may be beneficial to the overall population but harmful to some individuals, could be considered it would still be necessary to address whether this is justifiable from an ethical point of view or not.

### 7.2.9 Comparability of Results to other Research

According to the WHO [132], who evaluated some dengue vaccination models for a variety of epidemiological settings, most dengue models predict a reduction in severe dengue cases for epidemiological settings with a moderate to high transmission intensity. However, they also highlight that in very low transmission settings vaccination could lead to an increase in severe cases. In light of this it is interesting to consider the transmission intensity that was considered for each of the models in this thesis so as to determine how well the results can be compared

to other research. Note that the transmission intensity is generally considered low if at less than 50% of children at age 9 are seropositive, moderate if 50–70% at that age are seropositive and high for over 70% being seropositive at age 9 years.

The proportion of individuals who are seropositive in the absence of vaccination at a certain age can easily be obtained for each of the models presented in this thesis by considering that the proportion of individuals at age $a$ that are unaffected by serotype $i$ is given by $u_0^i(a)$. Therefore one can derive the proportion of individuals who have been affected by at least one serotype and are therefore seropositive to dengue as $p^+(a) = 1 - u_0^1(a)u_0^2(a)u_0^3(a)u_0^4(a)$. The intensities for the three models presented in this thesis are shown in Table 7.1.

Clearly the different assumptions and data used led to very different transmission settings. Considering a probability of being seropositive at age 9 years of almost 100% for the model with an age-dependent biting rate and a step-death function it is, for example, not surprising that the optimal vaccination ages for this model were generally far below 9 years. This is not true in the case of a vaccine-induced risk. However, in comparison to the other two models the optimal ages in this case still tend to be lower. Here it is again important to point out the limitations of the data that was used to derive the biting rate and thus the optimal vaccination ages. A rate of seropositives of 99% is surely a significant overestimation for Brazil and indeed most other countries albeit it may be applicable to some small communities with a very high transmission intensity.

The first model that was considered also corresponds to a high transmission setting. However, the proportion of seropositives at 9 years of 75% is much more similar to the transmission settings that are commonly modelled and assumed to benefit from vaccination. Indeed this was true in this thesis as well, especially for the risk of hospitalisation. Lethality is less frequently considered in other research. Lastly the model in which serological data was used to derive the biting rate and force of infection corresponds to a transmission setting which is barely moderate. In this case vaccination is generally assumed to be beneficial albeit not as drastically as in higher transmission settings [132]. Indeed the optimal vaccination ages were higher than for example with an age-dependent biting rate derived from mosquito biting data.

When comparing the optimal vaccination ages to those obtained from other models it is important to keep in mind that CRS (b) may be the best point of comparison. This is due to the fact that vaccination models for dengue often analyse the effect of vaccination in the presence of ADE. They usually consider successful

vaccination to correspond to a silent natural infection. In CRS (b) ADE is the base assumption and successful vaccination is considered to prime seronegative individuals due the increased risk in secondary infections. Note further that an additional vaccine-induced risk is not commonly explicitly modelled. However, the assumption of ADE and a priming of seronegatives due to vaccination of seronegatives does indeed already capture this to some extent.

Table 7.1: The proportion of seropositives at age 9 years for each of the three considered models together with the corresponding transmission intensity.

| Model assumptions | $p^+(9)$ | Intensity |
|---|---|---|
| $q$ and $\mu_H$ constant | 0.75 | high |
| $q(a)$ age-dependent, $\mu_H(a)$ step-function | 0.99 | very high |
| $q(a)$ from serological data, $\mu_H(a)$ step-function | 0.48 | low–moderate |

### 7.2.10 Summary

Vastly different optimal vaccination ages were obtained depending on the combination of assumptions made. In this section the factors influencing the optimal vaccination ages have been discussed. In particular the results are impacted by the complexity of the model, the risk that is being minimised through vaccination, the considered CRS, the vaccine efficacy and vaccine-induced risk as well as the restriction of the vaccination age according to the current licence.

The exact combination of all of these factors is decisive. This can clearly be seen when considering the two risk functions for the risk of hospitalisation and lethality. Depending on the underlying model assumptions the differences between the two functions has a large or almost no effect on the optimal vaccination age. However, for each of the functions the considered CRS was found to be one of the most important factors independent of the model assumptions. Considering that the CRSs correspond to some types of infection being risk-free this is not surprising. They are based on two common theories regarding the interaction of antibodies from different dengue serotypes, namely ADE and PCI. However, neither of these theories has been conclusively proven so far. Without more knowledge about the possible serotype interactions it is therefore difficult to determine the ideal age to vaccinate against dengue.

Another very important factor is whether Dengvaxia does indeed cause an increased risk in some recipients. In fact, this is closely related to the different CRSs since this increased risk is believed to be caused by vaccine-induced ADE.

The higher number of hospitalisations in seronegative recipients may therefore be understood as an indication that ADE does indeed influence the severity of infections. The most realistic CRSs may therefore be CRS (b) and CRS (d). However, clearly more research into the cross-reactions between naturally acquired antibodies to different serotypes and between naturally acquired and vaccine-induced antibodies is necessary in order to fully understand the disease dynamics and the effect vaccination may have on a specific recipient as well as on the population as a whole.

The analysis of the vaccine trial data based on the age-groups of children under the age of 9 years and those aged 9 years or above has been challenged. This is particularly important in light of the vaccine-induced risk which may in fact be solely associated with the serostatus of the recipient and not their age. Similarly the vaccine efficacy may not at all be age-dependent. However, the lower efficacy in individuals younger than 9 years is one of the reasons why the vaccine is currently only licensed for the use in children above the age of 9 years. This restriction tends to have a very negative impact depending on the underlying assumptions and may need to be revised.

With respect to the vaccine trial data, and indeed all data that was used to derive model parameters in this thesis, it needs to be kept in mind that there are limitations to its reliability. Consequently the derived vaccination ages merely give an indication and more analysis is necessary to give conclusive recommendations for the use of Dengvaxia.

Considering the large variety of optimal vaccination ages that were presented in this thesis and the uncertainties regarding antibody cross-reactions and vaccine performance it is clear that further research is necessary to enhance the reliability of the results. Some of the possible aspects future research could focus on will be discussed in the next section.

## 7.3 Future Work

Dengvaxia was licensed only recently and its long-term effects are not yet known. The controversy that arose after its licensing have, however, indicated that the vaccine may cause harm in participants who have not experienced a dengue infection prior to vaccination. In particular preliminary data from the long-term follow-up phase of three clinical trials documented an increased risk of severe dengue in break-through infections for such recipients. This data was therefore used in Chapters 5 and 6 of this thesis to attribute a vaccine-induced risk

dependent on the serostatus of a vaccinated individual. However, the data was very crude and it was necessary to estimate the true incidence of break-through cases in successfully vaccinated individuals. In addition, no data that detailed the increased risk dependent on the infecting serotype was available. A detailed analysis of the vaccination outcome in all recipients will be necessary in Brazil and the Philippines where large-scale campaigns had already been initiated before the dangers became apparent. In the future this may result in much more detailed data that should be incorporated to determine the optimal vaccination age. Even the crude data that was used in this thesis already showed a significant dependence of the optimal age on whether the vaccine induces a risk in seronegatives or not. Once more data becomes available the modelling framework as described in Chapter 3 can be utilised to determine more accurate optimal vaccination ages with a vaccine-induced risk.

However, independent of the available data it may be beneficial to adapt the transmission model and some underlying assumptions. In particular a multi-serotype model which explicitly models the vaccine-induced serostatus and the infection-induced serostatus may lead to a more realistic approximation of the infection and vaccination dynamics. Having said that, a model of all four dengue serotypes and the vaccination effect on the their transmission is going to be much more complex than the model presented in Chapter 3. In a first step it may therefore be easier to consider only two serotypes and their interactions explicitly. This can still lead to valuable insights into the vaccination effect since dengue serotypes appear to be pairwise similar in their dynamics [33]. Dengue models considering two serotypes are fairly common [85] and could be built upon to determine the optimal vaccination age similarly to how it was done in this thesis. A key point will be the definition of the lifetime expected risk for such a model which would certainly require separate definitions for the risk in vaccinated and unvaccinated individuals based on their serostatus.

The recommendations for the use of Dengvaxia have been adapted following the controversy about its effect in seronegative recipients. A two-serotype model should therefore also make it possible to restrict vaccination to seropositive individuals only. In the single-serotype model presented in this thesis such a restriction cannot easily be incorporated due to the transmission dynamics for each serotype being independent of each other. In a future two-serotype model it may, however, also make sense to analyse the effect of vaccinating a small proportion of seronegatives in addition to seropositives. This possibly reflects the reality more closely as laboratory tests are not 100% specific and even with prior

testing some seronegatives will likely be vaccinated.

Dengvaxia was the first licensed dengue vaccine. However, a number of other candidate vaccines are in late developmental stages with promising results in clinical trials. An analysis of the optimal vaccination age for these vaccines may be highly relevant considering that Dengvaxia has already been banned in a few countries due to the potential harm it causes in some recipients. In a first step this can be done using the modelling framework presented in this thesis with a number of small alterations, i.e. the number of recommended doses needs to be taken account of and the efficacy of the vaccine adjusted.

In any case a better understanding of the serotype interactions and the effect of dengue vaccines in seronegative and seropositive individuals is crucial for future work. For some vaccine candidates clinical trials are still ongoing and for Dengvaxia the long-term follow-up is now reaching its end. More reliable data concerning these aspects of dengue disease transmission and vaccination may therefore become available soon and could lead to an improvement of the results obtained through mathematical modelling in the future.

# References


[1] S. Abozeid, A. K. Elsayed, F. Schaffner, A. M. Samy, Re-emergence of *Aedes aegypti* in Egypt, The Lancet Infectious Diseases 18 (2018) 142–143.

[2] M. Aguiar, Dengue vaccination: a more ethical approach is needed, The Lancet 391 (2018) 1769–1770.

[3] M. Aguiar, S. B. Halstead, N. Stollenwerk, The impact of the newly licensed dengue vaccine in endemic countries, PLoS Neglected Tropical Diseases 10 (2016) e0005179.

[4] M. Aguiar, N. Stollenwerk, Dengvaxia: age as surrogate for serostatus, The Lancet Infectious Diseases 18 (2018) 245.

[5] M. Aguiar, N. Stollenwerk, Dengvaxia efficacy dependency on serostatus: a closer look at more recent data, Clinical Infectious Diseases 66 (2018) 641–642.

[6] M. Aguiar, N. Stollenwerk, S. B. Halstead, The risks behind Dengvaxia recommendation, The Lancet Infectious Diseases 16 (2016) 882–883.

[7] M. Amaku, F. Azevedo, M. N. Burattini, G. E. Coelho, F. A. B. Coutinho, D. Greenhalgh, L. Lopez, R. Motitsuki, A. Wilder-Smith, E. Massad, Magnitude and frequency variations of vector-borne infection outbreaks using the Ross–MacDonald model: explaining and predicting outbreaks of dengue fever, Epidemiology & Infection 144 (2016) 3435–3450.

[8] A. Amarasinghe, J. N. Kuritsky, G. W. Letson, H. S. Margolis, Dengue virus infection in Africa, Emerging Infectious Diseases 17 (2011) 1349.

[9] A. Amarasinghe, G. W. Letson, Dengue in the Middle East: a neglected,

emerging disease of importance, Transactions of the Royal Society of Tropical Medicine & Hygiene 106 (2012) 1–2.

[10] K. B. Anderson, R. V. Gibbons, D. A. Cummings, A. Nisalak, S. Green, D. H. Libraty, R. G. Jarman, A. Srikiatkhachorn, M. P. Mammen, B. Darunee, I.-K. Yoon, T. P. Endy, A shorter time interval between first and second dengue infections is associated with protection from clinical illness in a school-based cohort in Thailand, The Journal of Infectious Diseases 209 (2013) 360–368.

[11] R. M. Anderson, R. M. May, Infectious diseases of humans: dynamics and control, Oxford University Press, Oxford, UK, 1991.

[12] M. Andraud, N. Hens, C. Marais, P. Beutels, Dynamic epidemiological models for dengue transmission: a systematic review of structural approaches, PLoS One 7 (2012) e49085.

[13] F. E. Andre, R. Booy, H. L. Bock, J. Clemens, S. K. Datta, T. J. John, B. W. Lee, S. Lolekha, H. Peltola, T. Ruff, M. Santosham, H. J. Schmitt, Vaccination greatly reduces disease, disability, death and inequity worldwide, Bulletin of the World Health Organization 86 (2008) 140–146.

[14] H. Araújo, D. Carvalho, R. Ioshino, A. Costa-da Silva, M. Capurro, *Aedes aegypti* control strategies in Brazil: incorporation of new technologies to overcome the persistence of dengue epidemics, Insects 6 (2015) 576–594.

[15] V. E. M. de Araújo, J. M. T. Bezerra, F. F. Amâncio, V. M. de Azeredo Passos, M. Carneiro, Increase in the burden of dengue in Brazil and federated units, 2000 and 2015: analysis of the global burden of disease study 2015, Revista Brasileira de Epidemiologia 20 (2017) 205–216.

[16] Y. Arima, T. Matsui, Epidemiologic update of dengue in the Western Pacific region, 2010, Western Pacific Surveillance and Response Journal 2 (2011) 4.

[17] S. Bansal, B. T. Grenfell, L. A. Meyers, When individual behaviour matters: homogeneous and network models in epidemiology, Journal of the Royal Society Interface 4 (2007) 879–891.

[18] D. W. C. Beasley, A. D. T. Barret, The infectious agent, in: Tropical Medicine: Science and Practice | Dengue, eds: S. B. Halstead, G. Pasvol, S. L.

Hoffman, volume 5, Imperial College Press and World Scientific Publishing, London, 2008, pp. 29–74. doi:10.1142/p570.

[19] M. Begon, M. Bennett, R. G. Bowers, N. P. French, S. Hazel, J. Turner, A clarification of transmission terms in host-microparasite models: numbers, densities and areas, Epidemiology & Infection 129 (2002) 147–153.

[20] G. Benelli, C. L. Jeffries, T. Walker, Biological control of mosquito vectors: past, present, and future, Insects 7 (2016) 52.

[21] D. Bernoulli, Essai d'une nouvelle analyse de la mortalité causée par la petite vérole, et des avantages de l'inoculation pour la prévenir, Histoire de l'Académie Royale des Sciences, Mémoires Mathématiques et Physiques (1766) 1–45. *in French* (referenced in [145]).

[22] S. Bhatt, P. W. Gething, O. J. Brady, J. P. Messina, A. W. Farlow, C. L. Moyes, J. M. Drake, J. S. Brownstein, A. G. Hoen, O. Sankoh, M. F. Myers, D. B. George, T. Jaenisch, G. R. W. Wint, C. P. Simmons, T. W. Scott, J. J. Farrar, S. I. Hay, The global distribution and burden of dengue, Nature 496 (2013) 504–507.

[23] O. J. Brady, P. W. Gething, S. Bhatt, J. P. Messina, J. S. Brownstein, A. G. Hoen, C. L. Moyes, A. W. Farlow, T. W. Scott, S. I. Hay, Refining the global spatial limits of dengue virus transmission by evidence-based consensus, PLoS Neglected Tropical Diseases 6 (2012) e1760.

[24] I. A. Braga, D. Valle, *Aedes aegypti*: histórico do controle no Brasil, Epidemiologia e Serviços de Saúde 16 (2007) 113–118.

[25] Brasil. Ministério da Saúde, Sistema de Informação de Agravos de Notificação – Sinan: normas e rotinas, 2 ed., Ministério da Saúde, Secretaria de Vigilância em Saúde, Departamento de Vigilância Epidemiológica, Brasília, Brasil, 2007.

[26] Brasil. Ministério da Saúde, Ficha de investigação dengue e febre de chikungunya, Ministério da Saúde, Secretaria de Vigilância em Saúde, Departamento de Vigilância Epidemiológica, Brasília, Brasil, 2016. `http://portalsinan.saude.gov.br/images/documentos/Agravos/Dengue/Ficha_DENGCHIK_FINAL.pdf` (last accessed: July 1 2018).

[27] D. Buchillet, Dengue and dengue-like outbreaks in the past: The case of the Macau epidemic fever of 1874, Infection, Genetics and Evolution 12 (2012) 905–912.

[28] M. N. Burattini, Unpublished serological data collected before the introduction of Dengvaxia in Brazil, Personal Communication, 2017.

[29] M. N. Burattini, L. F. Lopez, F. A. B. Coutinho, J. B. Siqueira Jr, S. Homsani, E. Sarti, E. Massad, Age and regional differences in clinical presentation and risk of hospitalization for dengue in Brazil, 2000-2014, Clinics 71 (2016) 455–463.

[30] M. N. Burattini, E. Massad, Unpublished risk data relating to the risk due to dengue in Brazil, 2000-2014, Personal Communication, 2016.

[31] C. J. Burrell, C. R. Howard, F. A. Murphy, Fenner and White's Medical Virology, 5th ed., Academic Press, London, San Diego, Cambridge MA, Oxford, 2017, pp. 493–518.

[32] M. R. Capeding, N. H. Tran, S. R. S. Hadinegoro, H. I. H. J. M. Ismail, T. Chotpitayasunondh, M. N. Chua, C. Q. Luong, K. Rusmil, D. N. Wirawan, R. Nallusamy, P. Pitisuttithum, U. Thisyakorn, I. K. Yoon, D. van der Vliet, E. Langevin, T. Laot, Y. Hutagalung, C. Frago, M. Boaz, T. A. Wartel, N. G. Tornieporth, M. Saville, A. Bouckenooghe, the CYD14 Study Group, Clinical efficacy and safety of a novel tetravalent dengue vaccine in healthy children in Asia: a phase 3, randomised, observer-masked, placebo-controlled trial, The Lancet 384 (2014) 1358–1365.

[33] L. B. Carrington, C. P. Simmons, Human to mosquito transmission of dengue viruses, Frontiers in Immunology 5 (2014) Article No. 290.

[34] M. S. Chang, E. M. Christophel, D. Gopinath, R. M. Abdur, Challenges and future perspective for dengue vector control in the Western Pacific region, Western Pacific Surveillance and Response Journal 2 (2011) 9.

[35] R. Chen, N. Vasilakis, Dengue—quo tu et quo vadis?, Viruses 3 (2011) 1562–1608.

[36] S.-C. Chen, M.-H. Hsieh, Modeling the transmission dynamics of dengue fever: implications of temperature effects, Science of the Total Environment 431 (2012) 385–391.

[37] L. Coudeville, G. P. Garnett, Transmission dynamics of the four dengue serotypes in Southern Vietnam and the potential impact of vaccination, PLoS One 7 (2012) e51244.

[38] A. L. Dans, L. F. Dans, M. A. D. Lansang, M. A. A. Silvestre, G. H. Guyatt, Controversy and debate on dengue vaccine series-paper 1: review of a licensed dengue vaccine: inappropriate subgroup analyses and selective reporting may cause harm in mass vaccination programs, Journal of Clinical Epidemiology 95 (2018) 137.

[39] J. H. Diaz, Chemical and plant-based insect repellents: efficacy, safety, and toxicity, Wilderness & Environmental Medicine 27 (2016) 153–163.

[40] O. B. Dick, J. L. San Martín, R. H. Montoya, J. del Diego, B. Zambrano, G. H. Dayan, The history of dengue outbreaks in the Americas, The American Journal of Tropical Medicine and Hygiene 87 (2012) 584–593.

[41] O. Diekmann, J. A. P. Heesterbeek, J. A. Metz, On the definition and the computation of the basic reproduction ratio $R_0$ in models for infectious diseases in heterogeneous populations, Journal of Mathematical Biology 28 (1990) 365–382.

[42] Direct Council of the Pan American Health Organization, Resolution cd1.r1. continental *Aedes aegypti* eradication. Sept–Oct 1947 pub. 247, 3, 1947. `http://www.paho.org/English/GOV/CD/ftcd_1.htm#R1` (last accessed: October 12 2018).

[43] O. Dyer, Philippines halts dengue immunisation campaign owing to safety risk, The BMJ 359 (2017) j5759.

[44] W. J. Edmunds, N. J. Gay, M. Kretzschmar, R. Pebody, H. Wachmann, The pre-vaccination epidemiology of measles, mumps and rubella in Europe: implications for modelling studies, Epidemiology & Infection 125 (2000) 635–650.

[45] J. R. Egger, P. G. Coleman, Age and clinical dengue illness, Emerging Infectious Diseases 13 (2007) 924.

[46] R. A. Erickson, S. M. Presley, L. J. Allen, K. R. Long, S. B. Cox, A dengue model with a dynamic *Aedes albopictus* vector population, Ecological Modelling 221 (2010) 2899–2908.

[47] L. Esteva, C. Vargas, Coexistence of different serotypes of dengue virus, Journal of Mathematical Biology 46 (2003) 31–47.

[48] R. C. Fares, K. P. Souza, G. Añez, M. Rios, Epidemiological scenario of dengue in Brazil, BioMed Research International 2015 (2015) Article No. 321873.

[49] C. Farrington, Modelling forces of infection for measles, mumps and rubella, Statistics in Medicine 9 (1990) 953–967.

[50] C. Favier, N. Dégallier, M. G. Rosa-Freitas, J.-P. Boulanger, J. R. Costa Lima, J. F. Luitgards-Moura, C. E. Menkès, B. Mondet, C. Oliveira, E. T. S. Weimann, P. Tsouris, Early determination of the reproductive number for vector-borne diseases: the case of dengue in Brazil, Tropical Medicine & International Health 11 (2006) 332–340.

[51] N. M. Ferguson, I. Rodríguez-Barraquer, I. Dorigatti, L. Mier-y-Teran-Romero, D. J. Laydon, D. A. Cummings, Benefits and risks of the Sanofi-Pasteur dengue vaccine: Modeling optimal deployment, Science 353 (2016) 1033–1036.

[52] M. A. A. Figueiredo, L. C. Rodrigues, M. L. Barreto, J. W. O. Lima, M. C. Costa, V. Morato, R. Blanton, P. F. Vasconcelos, M. R. Nunes, M. G. Teixeira, Allergies and diabetes as risk factors for dengue hemorrhagic fever: results of a case control study, PLoS Neglected Tropical Diseases 4 (2010) e699.

[53] J. R. Fried, R. V. Gibbons, S. Kalayanarooj, S. J. Thomas, A. Srikiatkhachorn, I.-K. Yoon, R. G. Jarman, S. Green, A. L. Rothman, D. A. Cummings, Serotype-specific differences in the risk of Dengue Hemorrhagic Fever: an analysis of data collected in Bangkok, Thailand from 1994 to 2006, PLoS Neglected Tropical Diseases 4 (2010) e617.

[54] R. V. Gibbons, S. Kalanarooj, R. G. Jarman, A. Nisalak, D. W. Vaughn, T. P. Endy, M. P. Mammen, A. Srikiatkhachorn, Analysis of repeat hospital admissions for dengue to estimate the frequency of third or fourth dengue infections resulting in admissions and dengue hemorrhagic fever, and serotype sequences, The American Journal of Tropical Medicine and Hygiene 77 (2007) 910–913.

[55] R. V. Gibbons, M. Streitz, T. Babina, J. R. Fried, Dengue and US military operations from the Spanish–American War through today, Emerging Infectious Diseases 18 (2012) 623.

[56] D. Griffiths, A catalytic model of infection for measles, Applied Statistics (1974) 330–339.

[57] D. Gubler, The emergence of epidemic dengue fever and dengue hemorrhagic fever in the Americas: a case of failed public health policy, Pan American Journal of Public Health 17 (2005) 221.

[58] D. J. Gubler, Dengue and dengue hemorrhagic fever, Clinical Microbiology Reviews 11 (1998) 480–496.

[59] D. J. Gubler, M. Meltzer, Impact of dengue/dengue hemorrhagic fever on the developing world, Advances in Virus Research 53 (1999) 35–70.

[60] B. Guy, B. Barrere, C. Malinowski, M. Saville, R. Teyssou, J. Lang, From research to phase III: preclinical, industrial and clinical development of the Sanofi Pasteur tetravalent dengue vaccine, Vaccine 29 (2011) 7229–7241.

[61] B. Guy, O. Briand, J. Lang, M. Saville, N. Jackson, Development of the Sanofi Pasteur tetravalent dengue vaccine: One more step forward, Vaccine 33 (2015) 7100–7111.

[62] B. Guy, N. Jackson, Dengue vaccine: hypotheses to understand CYD-TDV-induced protection, Nature Reviews Microbiology 14 (2016) 45.

[63] A. Guzman, R. E. Istúriz, Update on the global spread of dengue, International Journal of Antimicrobial Agents 36 (2010) S40–S42.

[64] M. G. Guzman, E. Harris, Dengue, The Lancet 385 (2015) 453–465.

[65] M. G. Guzmán, G. Kouri, Dengue: an update, The Lancet Infectious Diseases 2 (2002) 33–42.

[66] S. R. Hadinegoro, J. L. Arredondo-García, M. R. Capeding, C. Deseda, T. Chotpitayasunondh, R. Dietze, H. I. H. J. M. Ismail, H. Reynales, K. Limkittikul, D. M. Rivera-Medina, H. N. Tran, A. Bouckenooghe, D. Chansinghakul, M. Cortés, K. Fanouillere, R. Forrat, C. Frago, S. Gailhardou, N. Jackson, F. Noriega, E. Plennevaux, T. A. Wartel, B. Zambrano, M. Saville, for the CYD-TDV Dengue Vaccine Working Group, Efficacy and

long-term safety of a dengue vaccine in regions of endemic disease, New England Journal of Medicine 373 (2015) 1195–1206.

[67] S. B. Halstead, Observations related to pathogensis of dengue hemorrhagic fever. VI. hypotheses and discussion, The Yale Journal of Biology and Medicine 42 (1970) 350.

[68] S. B. Halstead, Pathogenesis of dengue: challenges to molecular biology, Science 239 (1988) 476–481.

[69] S. B. Halstead, Neutralization and antibody-dependent enhancement of dengue viruses, Advances in Virus Research 60 (2003) 421.

[70] S. B. Halstead, Dengue in the Americas and Southeast Asia: do they differ?, Revista Panamericana de Salud Publica 20 (2006) 407–415.

[71] S. B. Halstead, Dengue: overview and history, in: Tropical Medicine: Science and Practice | Dengue, eds: S. B. Halstead, G. Pasvol, S. L. Hoffman, volume 5, Imperial College Press and World Scientific Publishing, London, 2008, pp. 1–28. doi:10.1142/p570.

[72] S. B. Halstead, Pathogenesis: Risk factors prior to infection, in: Tropical Medicine: Science and Practice | Dengue, eds: S. B. Halstead, G. Pasvol, S. L. Hoffman, volume 5, Imperial College Press and World Scientific Publishing, London, 2008, pp. 219–256. doi:10.1142/p570.

[73] S. B. Halstead, Antibodies determine virulence in dengue, Annals of the New York Academy of Sciences 1171 (2009) E48–E56.

[74] S. B. Halstead, Critique of World Health Organization recommendation of a dengue vaccine, Journal of Infectious Diseases: Perspectives 241 (2016) 1793–1795.

[75] S. B. Halstead, Dengvaxia sensitizes seronegatives to vaccine enhanced disease regardless of age, Vaccine 35 (2017) 6355–6358.

[76] W. M. Hammon, A. Rundnick, G. Sather, Viruses associated with epidemic hemorrhagic fevers of the Philippines and Thailand, Science 131 (1960) 1102–1103.

[77] N. Hens, M. Aerts, C. Faes, Z. Shkedy, O. Lejeune, P. Van Damme, P. Beutels, Seventy-five years of estimating the force of infection from current status data, Epidemiology & Infection 138 (2010) 802–812.

[78] N. Hens, Z. Shkedy, M. Aerts, C. Faes, P. Van Damme, P. Beutels, Modeling infectious disease parameters based on serological and social contact data: a modern statistical perspective, Statistics for Biology and Health, Book 63, Springer, New York (2012).

[79] H. W. Hethcote, Optimal ages of vaccination for measles, Mathematical Biosciences 89 (1988) 29–52.

[80] E. C. Holmes, S. S. Twiddy, The origin, emergence and evolutionary genetics of dengue virus, Infection, Genetics and Evolution 3 (2003) 19–28.

[81] O. Horstick, Y. Tozan, A. Wilder-Smith, Reviewing dengue: still a neglected tropical disease?, PLoS Neglected Tropical Diseases 9 (2015) e0003632.

[82] L. F. Jacintho, A. F. Batista, T. L. Ruas, M. G. Marietto, F. A. Silva, An agent-based model for the spread of the dengue fever: a swarm platform simulation approach, in: Proceedings of the 2010 Spring Simulation Multiconference, SpringSim 2010, Orlando, Florida, USA, Society for Computer Simulation International, 2010, p. 2.

[83] T. Jaenisch, T. Junghanss, B. Wills, O. J. Brady, I. Eckerle, A. Farlow, S. I. Hay, P. J. McCall, J. P. Messina, V. Ofula, A. Sall, A. Sakuntabhai, R. Velayudhan, G. R. W. Wint, H. Zeller, H. S. Margolis, O. Sankoh, the Dengue in Africa Study Group, Dengue expansion in Africa — not recognized or not happening?, Emerging Infectious Diseases 20 (2014). Online Report `https://wwwnc.cdc.gov/eid/article/20/10/14-0487_article` (last accessed: February 28 2019).

[84] A. Jain, U. C. Chaturvedi, Dengue in infants: an overview, FEMS Immunology and Medical Microbiology 59 (2010) 119–130.

[85] M. A. Johansson, J. Hombach, D. A. Cummings, Models of the impact of dengue vaccines: a review of current research and potential approaches, Vaccine 29 (2011) 5860–5868.

[86] J.-Y. Kang, J. Aldstadt, The influence of spatial configuration of residential area and vector populations on dengue incidence patterns in an individual-level transmission model, International Journal of Environmental Research and Public Health 14 (2017) 792.

[87] L. C. Katzelnick, L. Gresh, M. E. Halloran, J. C. Mercado, G. Kuan, A. Gordon, A. Balmaseda, E. Harris, Antibody-dependent enhancement of severe dengue disease in humans, Science 358 (2017) 929–932.

[88] W. O. Kermack, A. G. McKendrick, Contributions to the mathematical theory of epidemics. ii.—the problem of endemicity, Proceedings of the Royal Society A: Mathematical, Physical and Engineering Sciences 138 (1932) 55–83.

[89] R. Kimura, S. Hotta, Studies on dengue: anti-dengue active immunization experiments in mice, Japanese Journal of Bacteriology 1 (1944) 96–99. *in Japanese* (referenced in [27]).

[90] D. Knipl, S. M. Moghadas, The potential impact of vaccination on the dynamics of dengue infections, Bulletin of Mathematical Biology 77 (2015) 2212–2230.

[91] I. Kurane, Dengue hemorrhagic fever with special emphasis on immunopathogenesis, Comparative Immunology, Microbiology & Infectious Diseases 30 (2007) 329–340.

[92] H. J. Larson, K. Hartigan-Go, A. de Figueiredo, Vaccine confidence plummets in the Philippines following dengue vaccine scare: why it matters to pandemic preparedness, Human Vaccines & Immunotherapeutics (2018) 1–3.

[93] A. S.-Y. Leong, K. T. Wong, T. Y.-M. Leong, P. H. Tan, P. Wannakrairot, The pathology of dengue hemorrhagic fever, Seminars in Diagnostic Pathology 24 (2007) 227–236.

[94] J. K. Lim, M. Carabali, J.-S. Lee, K.-S. Lee, S. Namkung, S.-K. Lim, V. Ridde, J. Fernandes, B. Lell, S. H. Matendechero, M. Esen, E. Andia, N. Oyembo, A. Barro, E. Bonnet, S. M. Njenga, S. T. Agnandji, S. Yaro, N. Alexander, I.-K. Yoon, Evaluating dengue burden in Africa in passive fever surveillance and seroprevalence studies: protocol of field studies of the dengue vaccine initiative, BMJ Open 8 (2018) e017673.

[95] L. F. Lopez, M. Amaku, F. A. B. Coutinho, M. Quam, M. N. Burattini, C. J. Struchiner, A. Wilder-Smith, E. Massad, Modeling importations and exportations of infectious diseases via travelers, Bulletin of Mathematical Biology 78 (2016) 185–209.

[96] J. Lourenço, M. Recker, Natural, persistent oscillations in a spatial multi-strain disease system with application to dengue, PLoS Computational Biology 9 (2013) e1003308.

[97] G. MacDonald, The epidemiology and control of malaria. 1957, London: Oxford University Press (1957).

[98] S. Mandal, R. R. Sarkar, S. Sinha, Mathematical models of malaria-a review, Malaria Journal 10 (2011) 202.

[99] E. Massad, Biting Rate Data, Personal Communication, 2015.

[100] E. Massad, M. Amaku, F. A. B. Coutinho, C. J. Struchiner, M. N. Burattini, K. Khan, J. Liu-Helmersson, J. Rocklöv, M. U. Kraemer, A. Wilder-Smith, Estimating the probability of dengue virus introduction and secondary autochthonous cases in Europe, Scientific Reports 8 (2018) 4629.

[101] E. Massad, M. Amaku, F. A. B. Coutinho, C. J. Struchiner, L. F. Lopez, A. Wilder-Smith, M. N. Burattini, Estimating the size of *Aedes aegypti* populations from dengue incidence data: Implications for the risk of yellow fever outbreaks, Infectious Disease Modelling 2 (2017) 441–454.

[102] E. Massad, F. Coutinho, M. Burattini, M. Amaku, Estimation of $R_0$ from the initial phase of an outbreak of a vector-borne infection, Tropical Medicine & International Health 15 (2010) 120–126.

[103] E. Massad, F. A. B. Coutinho, M. N. Burattini, L. F. Lopez, The risk of yellow fever in a dengue-infested area, Transactions of the Royal Society of Tropical Medicine & Hygiene 95 (2001) 370–374.

[104] H. McCallum, N. Barlow, J. Hone, How should pathogen transmission be modelled?, Trends in Ecology & Evolution 16 (2001) 295–300.

[105] J. P. Messina, O. J. Brady, T. W. Scott, C. Zou, D. M. Pigott, K. A. Duda, S. Bhatt, L. Katzelnick, R. E. Howes, K. E. Battle, C. P. Simmons, S. I. Hay, Global spread of dengue virus types: mapping the 70 year history, Trends in Microbiology 22 (2014) 138–146.

[106] A. H. Mohd-Zaki, J. Brett, E. Ismail, M. L'Azou, Epidemiology of dengue disease in Malaysia (2000–2012): a systematic literature review, PLoS Neglected Tropical Diseases 8 (2014) e3159.

[107] H. Muench, Derivation of rates from summation data by the catalytic curve, Journal of the American Statistical Association 29 (1934) 25–38.

[108] M. Mustafa, V. Rasotgi, S. Jain, V. Gupta, Discovery of fifth serotype of dengue virus (denv-5): A new public health dilemma in dengue control, Medical Journal Armed Forces India 71 (2015) 67–70.

[109] Y. Nagao, K. Koelle, Decreases in dengue transmission may act to increase the incidence of dengue hemorrhagic fever, Proceedings of the National Academy of Sciences 105 (2008) 2238–2243.

[110] F. Narvaez, G. Gutierrez, M. A. Pérez, D. Elizondo, A. Nuñez, A. Balmaseda, E. Harris, Evaluation of the traditional and revised WHO classifications of dengue disease severity, PLoS Neglected Tropical Diseases 5 (2011) e1397.

[111] H. Nishiura, Duration of short-lived cross-protective immunity against a clinical attack of dengue: A preliminary estimate, Dengue Bulletin (2008) 55–66.

[112] H. Nobuchi, The symptoms of a dengue-like illness recorded in a Chinese medical encyclopedia, Kanpo Rinsho 26 (1979) 422–425. *in Japanese* (referenced in [58]).

[113] D. Normile, Surprising new dengue virus throws a spanner in disease control efforts, Science 342 (2013) 415.

[114] M. R. T. Nunes, N. R. Faria, H. B. Vasconcelos, D. B. de Almeida Medeiros, C. P. Silva de Lima, V. L. Carvalho, E. V. Pinto da Silva, J. F. Cardoso, E. C. Sousa Jr, K. N. B. Nunes, S. G. Rodrigues, A. B. Abecasis, M. A. Suchard, P. Lemey, P. F. Vasconcelos, Phylogeography of dengue virus serotype 4, Brazil, 2010-2011, Emerging Infectious Diseases 18 (2012) 1858–1864.

[115] S. Olkowski, B. M. Forshey, A. C. Morrison, C. Rocha, S. Vilcarromero, E. S. Halsey, T. J. Kochel, T. W. Scott, S. T. Stoddard, Reduced risk of disease during post-secondary dengue virus infections, Journal of Infectious Diseases 208 (2013) 1026–1033.

[116] E.-E. Ooi, D. J. Gubler, Dengue in Southeast Asia: epidemiological characteristics and strategic challenges in disease prevention, Cadernos de Saude Publica 25 (2009) S115–S124.

[117] W. A. Orenstein, K. Seib, D. Graham-Rowe, S. Berkley, Contemporary vaccine challenges: improving global health one shot at a time, Science Translational Medicine 6 (2014) 253ps11.

[118] E. L. Pang, H.-S. Loh, Towards development of a universal dengue vaccine–how close are we?, Asian Pacific Journal of Tropical Medicine 10 (2017) 220–228.

[119] W. G. van Panhuis, C. Luxemburger, K. Pengsaa, K. Limikittikul, A. Sabchareon, J. Lang, A. P. Durbin, D. A. T. Cummings, Decay and persistence of maternal dengue antibodies among infants in Bangkok, American Society of Tropical Medicine and Hygiene 85 (2011) 355–362.

[120] T. A. Perkins, R. C. Reiner, Q. A. ten Bosch, G. España, A. Verma, K. A. Liebman, V. A. Paz-Soldan, J. P. Elder, A. C. Morrison, S. T. Stoddard, U. Kitron, G. M. Vazquez-Prokopec, T. W. Scott, D. L. Smith, Statistical and biological uncertainties associated with vaccine efficacy estimates and their implications for dengue vaccine impact projections, bioRxiv (2016).

[121] P. Pongsumpun, I. Tang, Transmission of dengue hemorrhagic fever in an age structured population, Mathematical and Computer Modelling 37 (2003) 949–961.

[122] H. R. Rathor, The role of vectors in emerging and re-emerging diseases in the Eastern Mediterranean region, Eastern Mediterranean Health Journal 2 (1996) 61–67.

[123] W. Reed, J. Carroll, A. Agramonte, J. W. Lazear, The etiology of yellow fever—a preliminary note, Public Health Papers and Reports 26 (1900) 37.

[124] N. G. Reich, S. Shrestha, A. A. King, P. Rohani, J. Lessler, S. Kalayanarooj, I.-K. Yoon, R. V. Gibbons, D. S. Burke, D. A. Cummings, Interactions between serotypes of dengue highlight epidemiological impact of cross-immunity, Journal of the Royal Society Interface 10 (2013).

[125] G. Rezza, Dengue and other *Aedes*-borne viruses: a threat to Europe?, Eurosurveillance 21 (2016) 30238.

[126] S. Riedel, Edward Jenner and the history of smallpox and vaccination, in: Baylor University Medical Center Proceedings, volume 18, Taylor & Francis, 2005, pp. 21–25.

[127] R. Ross, The prevention of malaria, John Murray; London, 1911.

[128] B. Rush, An account of the bilious remitting fever: As it appeared in Philadelphia, in the summer and autumn of the year 1780, The American Journal of Medicine 11 (1951) 546–550.

[129] A. Sabchareon, D. Wallace, C. Sirivichayakul, K. Limkittikul, P. Chanthavanich, S. Suvannadabba, V. Jiwariyavej, W. Dulyachai, K. Pengsaa, T. A. Wartel, A. Moureau, M. Saville, A. Bouckenooghe, S. Viviani, N. G. Tornierporth, J. Lang, Protective efficacy of the recombinant, live-attenuated, CYD tetravalent dengue vaccine in Thai schoolchildren: a randomised, controlled phase 2b trial, The Lancet 380 (2012) 1559–1567.

[130] A. B. Sabin, Research on dengue during World War II, The American Journal of Tropical Medicine and Hygiene 1 (1952) 30–50.

[131] A. B. Sabin, R. W. Schlesinger, Production of immunity to dengue with virus modified by propagation in mice, Science 101 (1945) 640–642.

[132] SAGE Working Group on Dengue Vaccines and WHO Secretariat, Background paper on dengue vaccines, World Health Organization, Geneva, Switzerland, 2016.

[133] SAGE Working Group on Dengue Vaccines and WHO Secretariat, Background paper on dengue vaccines - Revision of the background paper from 17 March 2016, World Health Organization, Geneva, Switzerland, 2018.

[134] T. S. Salles, T. da Encarnação Sá-Guimarães, E. S. L. de Alvarenga, V. Guimarães-Ribeiro, M. D. F. de Meneses, P. F. de Castro-Salles, C. R. dos Santos, A. C. do Amaral Melo, M. R. Soares, D. F. Ferreira, M. F. Moreira, History, epidemiology and diagnostics of dengue in the American and Brazilian contexts: a review, Parasites & Vectors 11 (2018) 264.

[135] Sanofi Pasteur Communication, Sanofi Pasteur communication on SAGE recommendation about Dengvaxia® dengue vaccine, 2018. http://mediaroom.sanofi.com/sanofi-pasteur-communication-on-sage-recommendation-about-dengvaxia-dengue-vaccine/ (last accessed: December 1 2018).

[136] Sanofi Pasteur Press Release, Dengvaxia®, World"s first dengue vaccine, approved in Mexico, 2015. https://www.sanofipasteur.com/-/

media/Project/One-Sanofi-Web/Websites/Global/Sanofi-Pasteur-COM/Home/en/media-room/docs/PR_20151209_FirstDengueVaccin_ApprovedInMexico_EN.pdf (last accessed: December 1 2018).

[137] Sanofi Pasteur Press Release, Dengue immunization public program in Paraná State of Brazil set to achieve WHO 2020 ambition, 2016. https://www.sanofipasteur.com/-/media/Project/One-Sanofi-Web/Websites/Global/Sanofi-Pasteur-COM/Home/en/media-room/docs/PR_20160813_DengueImmunizationPubicProgramInParana_EN.pdf (last accessed: December 1 2018).

[138] Sanofi Pasteur Press Release, World's first public dengue immunization program starts in the Philippines, 2016. https://www.sanofipasteur.com/-/media/Project/One-Sanofi-Web/Websites/Global/Sanofi-Pasteur-COM/Home/en/media-room/docs/PR_20160404_WorldFirstPublicDengueImmunizationProgramInPhilippines_EN.pdf (last accessed: December 1 2018).

[139] Sanofi Pasteur Press Release, Sanofi updates information on dengue vaccine, 2017. https://mediaroom.sanofi.com/-/media/Project/One-Sanofi-Web/Websites/Global/Sanofi-COM/mediaroom/pdf/2017/2017-11-29-EN.pdf (last accessed: December 1 2018).

[140] F. Schaffner, A. Mathis, Dengue and dengue vectors in the WHO European region: past, present, and scenarios for the future, The Lancet Infectious Diseases 14 (2014) 1271–1280.

[141] J. Schmidt-Chanasit, M. Haditsch, I. Schöneberg, S. Günther, K. Stark, C. Frank, Dengue virus infection in a traveller returning from Croatia to Germany, Eurosurveillance 15 (2010) 19677.

[142] J. Schneider, D. Droll, A timeline for dengue in the Americas to December 31, 2000 and noted first occurrences, Pan American Health Organization (2001).

[143] D. S. Shepard, E. A. Undurraga, Y. A. Halasa, Economic and disease burden of dengue in Southeast Asia, PLoS Neglected Tropical Diseases 7 (2013) e2055.

[144] B. de la C. Sierra, G. Kouri, M. Guzman, Race: a risk factor for dengue hemorrhagic fever, Archives of Virology 152 (2007) 533.

[145] C. I. Siettos, L. Russo, Mathematical modeling of infectious disease dynamics, Virulence 4 (2013) 295–306.

[146] D. Siregar, I. M. Djadja, R. Arminsih, Analysis of the risk factors of dengue hemorrhagic fever (DHF) in rural populations in Panongan subdistrict, Tangerang 2016, in: The 1st International Conference on Global Health, November 2017, Jakarta, Indonesia, Health Sciences Cluster of Indonesia, eds: B. Utoma, Sabarinah, O. Kaewboonchoo, volume 4, KnE Life Sciences, 2018, pp. 119–128.

[147] A. Srikiatkhachorn, A. L. Rothman, R. V. Gibbons, N. Sittisombut, P. Malasit, F. A. Ennis, S. Nimmannitya, S. Kalayanarooj, Dengue—how best to classify it, Clinical Infectious Diseases 53 (2011) 563–567.

[148] J. Stoler, R. al Dashti, F. Anto, J. N. Fobil, G. A. Awandare, Deconstructing "malaria": West Africa as the next front for dengue fever surveillance and control, Acta Tropica 134 (2014) 58–65.

[149] T. Succo, I. Leparc-Goffart, J.-B. Ferré, D. Roiz, B. Broche, M. Maquart, H. Noel, O. Catelinois, F. Entezam, D. Caire, F. Jourdan, I. Esteve-Moussion, A. Cochet, C. Paupy, C. Rousseau, M. C. Paty, F. Golliot, Autochthonous dengue outbreak in Nîmes, South of France, July to September 2015, Eurosurveillance 21 (2016) 30240.

[150] A. Supriatna, E. Soewono, S. A. van Gils, A two-age-classes dengue transmission model, Mathematical Biosciences 216 (2008) 114–121.

[151] C.-Y. Tsai, K. Lee, C.-H. Lee, K. D. Yang, J.-W. Liu, Comparisons of dengue illness classified based on the 1997 and 2009 World Health Organization dengue classification schemes, Journal of Microbiology, Immunology and Infection 46 (2013) 271–281.

[152] S. S. Twiddy, E. C. Holmes, A. Rambaut, Inferring the rate and timescale of dengue virus evolution, Molecular Biology and Evolution 20 (2003) 122–129.

[153] United States Central Intelligence Agency, Brazil - The World Factbook, 2016. `https://www.cia.gov/library/publications/the-world-factbook/geos/br.html` (last accessed: November 21 2016).

[154] N. Vasilakis, J. Cardosa, K. A. Hanley, E. C. Holmes, S. C. Weaver, Fever from the forest: prospects for the continued emergence of sylvatic dengue

virus and its impact on public health, Nature Reviews Microbiology 9 (2011) 532.

[155] C. Vicente, C. C. Junior, G. Fröschl, C. Romano, A. Cabidelle, K.-H. Herbinger, Influence of demographics on clinical outcome of dengue: a cross-sectional study of 6703 confirmed cases in Vitória, Espírito Santo State, Brazil, Epidemiology & Infection 145 (2017) 46–53.

[156] L. Villar, G. H. Dayan, J. L. Arredondo-García, D. M. Rivera, R. Cunha, C. Deseda, H. Reynales, M. S. Costa, J. O. Morales-Ramírez, G. Carrasquilla, L. C. Rey, R. Dietze, K. Luz, R. E, M. C. M. Montoya, M. C. Supelano, B. Zambrano, E. Langevin, M. Boaz, N. Tornieporth, M. Saville, F. Noriega, for the CYD15 Study Group, Efficacy of a tetravalent dengue vaccine in children in Latin America, New England Journal of Medicine 372 (2015) 113–123.

[157] E. Wang, H. Ni, R. Xu, A. D. Barrett, S. J. Watowich, D. J. Gubler, S. C. Weaver, Evolutionary relationships of endemic/epidemic and sylvatic dengue viruses, Journal of Virology 74 (2000) 3227–3234.

[158] T. A. Wartel, A. Prayitno, S. Hadinegoro, M. R. Capeding, U. Thisyakorn, N. H. Tran, A. Moureau, A. Bouckenooghe, J. Nealon, A.-F. Taurel, Three decades of dengue surveillance in five highly endemic South East Asian countries: A descriptive review, Asia Pacific Journal of Public Health 29 (2017) 7–16.

[159] F. Were, The dengue situation in Africa, Paediatrics and International Child Health 32 (2012) 18–21.

[160] WHO Regional Office for Europe, Infectious diseases in a changing climate – Dengue in the WHO European region, 2013. http://www.euro.who.int/__data/assets/pdf_file/0009/234198/Dengue-in-the-WHO-European-Region.pdf (last accessed: October 28 2018).

[161] P. S. Wikramaratna, C. P. Simmons, S. Gupta, M. Recker, The effects of tertiary and quaternary infections on the epidemiology of dengue, PLoS One 5 (2010) e12347.

[162] A. Wilder-Smith, E. Schwartz, Dengue in travelers, New England Journal of Medicine 353 (2005) 924–932.

[163] World Health Organization, Manual on environmental management for mosquito control, with special emphasis on malaria vectors, World Health Organization, Geneva, Switzerland, 1982.

[164] World Health Organization, Dengue hemorrhagic fever: diagnosis, treatment, prevention and control, World Health Organization, Geneva, Switzerland, 1997.

[165] World Health Organization, Dengue: guidelines for diagnosis, treatment, prevention and control, World Health Organization, Geneva, Switzerland, 2009.

[166] World Health Organization, Global strategy for dengue prevention and control 2012-2020, World Health Organization, Geneva, Switzerland, 2012.

[167] World Health Organization, Fact sheet - dengue and severe dengue, 2018. `http://www.who.int/news-room/fact-sheets/detail/dengue-and-severe-dengue` (last accessed: October 27 2018).

[168] World Health Organization Regional Offices for South-East Asia and the Western Pacific, The dengue strategic plan for the Asia Pacific Region 2008-2015, 2008. `http://www.wpro.who.int/mvp/Dengue_Strategic_Plan.pdf` (last accessed: October 27 2018).

[169] J. Wunderlich, R. Acuna-Soto, W. Alonso, Dengue hospitalisations in Brazil: annual wave from West to East and recent increase among children, Epidemiology & Infection 146 (2018) 236–245.

[170] R. Ximenes, M. Amaku, L. F. Lopez, F. A. B. Coutinho, M. N. Burattini, D. Greenhalgh, A. Wilder-Smith, C. J. Struchiner, E. Massad, The risk of dengue for non-immune foreign visitors to the 2016 summer Olympic Games in Rio de Janeiro, Brazil, BMC Infectious Diseases 16 (2016) Article No. 186.

[171] L. Xue, X. Fang, J. M. Hyman, Comparing the effectiveness of different strains of *Wolbachia* for controlling chikungunya, dengue fever, and zika, PLoS Neglected Tropical Diseases 12 (2018) e0006666.

[172] P. M. Zanotto, E. A. Gould, G. F. Gao, P. H. Harvey, E. C. Holmes, Population dynamics of flaviviruses revealed by molecular phylogenies, Proceedings of the National Academy of Sciences 93 (1996) 548–553.